THE AMERICAN JOURNAL OF PATHOLOGY

VOLUME IV JANUARY, 1928 NUMBER 1

THE PATHOLOGY OF BILHARZIASIS *

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BILHARZIA; OBSERVATIONS ON ITS PATHOLOGY

Egyptian hematuria has been known from the very earliest times. Bilharz, working in Egypt in 1831, discovered a trematode worm in the mesenteric vessels of men who suffered from this disease and gave us the first accurate description of the parasites. In 1894, Looss[10] described the parasites more fully and outlined the life cycle in the human body. The mode of transfer from patient to patient was not fully investigated until Leiper,[9] working in the bilharzia mission in Egypt in 1915, discovered that in common with other parasitic trematodes, the bilharzia parasite is transmitted from host to host through an intermediate host. In this case the intermediate hosts are small fresh water snails of the genus bullinus and genus planorbis.

There are three closely related trematodes of the genus Schistosoma that are now known to produce characteristic lesions in man. *Schistosoma japonicum* occurs in the far East. The other two, *Schistosoma mansoni* and *Schistosoma hematobium* occur in Egypt and along the eastern coast of Africa to the Cape. The disease is found all along northern Africa and in the Congo, but most commonly in Egypt. It occurs in the West Indies and in Central America. Throughout the rest of the world occasional cases occur, but they are usually imported from some area where the disease is endemic. The disease is limited in its distribution by the distribution of the intermediate host and the habits of the people with regard to exposure to water that is contaminated.

* Received for publication July 25, 1927.

Conditions in the Nile valley, particularly in the delta region, are peculiarly favorable to the distribution and propagation of the bilharzia parasite. The congestion of population and primitive habits of the people insure gross contamination of the water; the tropical climate and perennial irrigation insure a wide distribution of the intermediate hosts of the parasite, and the agricultural habits of the people insure the adequate exposure of the skin to water containing infective forms of the parasite. For these reasons the incidence of infestation in a land like Egypt is very high, particularly among the peasantry.

Ferguson [7] in 1913 stated that in more than 600 postmortems on male subjects, performed in the medical school in Egypt, no less than 61 per cent of the males between 5 and 40 years of age were infested. Madden [12] in 1910 said that 10 per cent of the total mortality in Egypt was due to bilharzia. He points out the fact that his figures are based on the number of deaths occurring in the hospital, and as very many ill patients go home to die, and are therefore not included in the record, the percentage is undoubtedly much higher. Of 3485 native patients treated in the American Hospital at Tanta since 1924, 35.3 per cent were treated for bilharzia and its complications. The incidence of the disease among the peasantry of the country is much higher than these figures indicate, for there are patients with mild infection who complain of no symptoms and yet occasionally pass blood and ova in the urine and feces.

The American Mission Hospital is situated at almost the geographic center of the delta of the Nile and affords an ideal opportunity to see a large amount of bilharzial material both clinically and in the laboratory. Approximately 1200 native patients are housed for periods varying from one to three weeks during each year. A large number of these patients come suffering from advanced bilharziasis. Surgical intervention is often necessary for the relief of complications arising from the infestation. The material from which this study was made was collected over a period of five years residence in Tanta. All specimens removed surgically were examined and the more interesting of them preserved in 10 per cent formalin and brought to America for further study. They were cut, embedded in paraffin, sectioned, and stained with hematoxylin and eosin in the laboratory of the City Hospital in Cleveland.

All of the specimens were from native Egyptians and contained

bilharzia parasites. Many of them were polypi removed from the rectum and bladder. In many cases of inguinal hernia, the peritoneal sac was found to be infiltrated with ova. Where this was the case the sacs were kept for study. In the course of laparotomies for bilharzial tumors, specimens were removed from the abdomen. These specimens consisted of markedly involved epiploic appendages, pieces of omentum and peritoneum containing nodules of ova. In cases where the vermiform appendix was removed from native patients, it was always examined for bilharzial and amebic infections. Interesting specimens showing bilharzia in the female genital tract were obtained during the course of gynecological operations for other than bilharzial conditions. The effects of oviposition under the squamous epithelium of the vagina were studied in sections obtained from cases of marked vaginal polyposis by means of the curette. Sections from the margins of perineal fistulae near the anus and about the scrotum were used to study the effects of ovaposition under the true skin. Four partial autopsies on patients who died in the hospital furnished the rest of the material.

The study is based, specifically, on a series of sixty-five specimens that show the intestinal mucosa; fourteen specimens of tissue including the peritoneum; twelve vermiform appendices, and forty other tissues from various parts of the body. All of the tissues in this series showed bilharzial involvement.

In order to understand the pathology of bilharzia, it is necessary to know the life history of the parasite that causes it. In general the two species known in Egypt are very similar and one description will, for our purpose, suffice for both. A more detailed description is found in "The Practice of Medicine in the Tropics" by Byam and Archibald.

The Life History of the Parasite

The animal is a bisexual trematode. The male is a white to gray worm, 1 to 1.5 cm. long. The anterior portion of the body is cylindrical and is armed with an anterior and ventral sucker. The portion of the body posterior to the ventral sucker is leaf-like when spread out and terminates in a rounded blunt extremity. In the natural condition this flattened posterior portion of the body is rolled in from the two sides, forming a longitudinal ventral groove, the gynecaproic canal. The result is a rounded appearance. (Figs. 1 and 5.)

The female parasite is filamentous, cylindrical in shape and much longer than the male. Two suckers, similar to those described for the male, are seen toward the anterior end of the body. In nature the female is usually partially enveloped by the male and lies in the gynecaproic canal (Figs. 2, 3, 4). Both the male and the female parasite have a very primitive alimentary canal beginning at a stoma in the anterior end of the body and ending blindly posteriorly. The anatomy of the generative organs differs somewhat in the different species, but in general is similar. The ovary is located in the posterior half of the female worm and the oviduct passes forward to join the vitelline duct. The uterus extends anteriorly to the genital pore, just posterior to the ventral sucker.

The ova measure about 0.15 by 0.06 mm. and are just about the lower limits of visibility to the naked eye. Those of the species hematobium have a terminal spine (Fig. 13), and those of the genus mansoni have a lateral spine (Fig. 8).

The parasites attain their adult form in the liver and vessels of the portal system. When mature they migrate against the blood stream till they reach a capillary bed. Selection is apparent in that *S. mansoni* migrate to the capillary bed under the mucosa of the colon and rectum, and *S. hematobium* to the mucosa of the urogenital tract, particularly of the bladder.

In Tanta, Egypt, where these observations were made, double infections are common, and *S. hematobium* ova (terminal spined) are commonly found in the feces associated with the ova of *S. mansoni* (lateral spined). Dew,[3] has pointed out the ease with which females of *S. hematobium* can migrate through the veins of the pelvic plexus to the region of the lower rectum and anus, in explanation of this fact. Fairley,[4] has pointed out the frequency with which *S. hematobium* ova occur in the feces of patients who are not infected with *S. mansoni*. *S. mansoni* ova occur in the urine, but only in heavy infestations and much less commonly than in the feces. In the year 1926 a record was kept of the routine feces and urine examinations that were made in Tanta Hospital. Many of these were single examinations and therefore the results cannot be taken as indicating the total incidence of infestation. The results are interesting in that they give an index to the relative frequency with which the two types of parasite occur in the branches of the pelvic venous plexus and the inferior mesenteric veins (Table I).

In the study of tissues the selective deposition of ova is still more clearly evident. Both in cut sections and in tissues digested by 5 per cent alkali the general region from which the tissues come can be determined by the character of the ova present. In tissues from the bladder, lower third of the ureters, urethra and genitalia, practically all of the ova in the cases studied in this series were terminal

TABLE 1

Examinations Showing Distribution of Ova in Urine and Feces

Number of Feces Examinations 860		Number of Urine Examinations 888	
Positive for *S. mansoni*	Positive for *S. hematobium*	Positive for *S. mansoni*	Positive for *S. hematobium*
267 or 31%	31 or 3.6%	20 or 2.2%	302 or 22.8%

spined. In tissues from the rectum, around the anus and in the vagina, both lateral and terminal spined ova were found, the former predominating. In the mucosa of the colon, in the parietal and visceral peritoneum, retroperitoneal lymph nodes, spleen and liver, lateral spined ova greatly out-numbered the ova of *S. hematobium* and in many cases the latter were not found.

In oviposition the female parasite forces the anterior end of her body into the smaller capillaries as far as she can and then deposits her ova. The ova are left in the dilated capillary space as the female withdraws. The elastic vessel walls close down on the ovum, forcing its sharp spine against the wall. The abrasion and a peculiar irritating quality that the ovum seems to possess cause a severe inflammatory reaction, swelling of the tissue, and finally ulceration of the epithelial covering, allowing the ovum to escape into the bladder or gut as the case may be. In a land like Egypt the ovum then readily passes into the water of the canals and streams.

The ovum itself is innocent of any ability to infest a new human host either by contact or by ingestion. If allowed to dry, it quickly perishes, but in fresh water it hatches almost at once into a miracidium. This is a unicellular ciliated form in some ways resembling a paramecium. It swims around rapidly in water but quickly perishes if it does not find a suitable host. Such hosts abound in the waters of Egypt. The fresh water snails of the genus bullinus and genus

planorbis are readily attacked and infected. Four to five weeks after infestation of the snail there emerge from its body cercariae. These are small tadpole-like forms that are just about visible to the naked eye and can be seen easily with the hand lens. This form swims about in the water for from twenty-four to thirty-six hours. Before the end of this time they must find a new human host or they perish. Contact of water harboring this form of the parasite with any surface of the body or the mucous membranes of the mouth and throat leads to infestation. The cercariae attach themselves to the skin or mucous membrane by means of their suckers, lose their tails, and penetrate to the subcutaneous lymphatics. They then start on a course of migration in the body and in about six weeks the adult forms may be found in the liver and portal veins, completing the life cycle (Leiper[9]).

It is not known just how long the parasites continue to live and produce eggs in the tissues of the host. It is evidently quite a long period, perhaps years. It is certain that individuals who have long been away from sources of infestation in countries where the disease does not exist still pass living ova in the urine and feces. In one case, known to the author, a young Egyptian student who contracted the disease when a boy continued to pass living ova during the years of his study of medicine in America and was still passing them when he returned to Egypt.

Clinical Manifestations

When the initial infection occurs there is a definite irritation of the skin due to the passage of the parasites. This is perhaps more marked in Japan than Egypt. At any rate, it has been described by Japanese writers who study the skin lesions in those who work in the rice paddies. In Egypt, skin lesions are seldom noticed and the patient does not seek medical aid because of them. As a rule, too, the infestation is so gradually acquired that the skin lesions are neither very widespread nor extensive at any one time. As the parasite penetrates into the deeper tissues, a small inflammatory nodule may be felt for a short time. Leiper describes an inflammatory skin lesion occurring in experimental animals exposed to bilharzial cercariae.

If only a few parasites have found an entrance to the body in a given exposure, the invasion is not attended by subjective symptoms.

If a massive invasion occurs there will be fever and malaise (Fairley[4]). In one case in our experience where a patient had been kept away from his home environment until he was free from infestation, and then allowed to return to his village, he went to work irrigating the fields and was exposed to heavy bilharzia infestation. A few weeks later he began to suffer from a severe typhoid-like fever with jaundice and marked prostration. Enteric fevers were ruled out by serologic tests and on clinical grounds. As he gradually recovered from his febrile attack, he developed symptoms of severe generalized abdominal bilharziasis with both types of ova in the urine and feces. A similar febrile course during invasion by the parasites has been described in foreign soldiers who have bathed in the canals of Egypt (Fairley[4]), and in sailors who, while on leave, bathed in fresh water lakes in China (Laning[8]).

In most cases the infestation of the individual begins in early childhood and continues throughout life. The peasantry are constantly exposed and constantly adding to their parasitization. If the number of parasites is not excessive, the host is able to bear his infestation fairly well, but when the infestation is excessive or complications set in, he succumbs.

PATHOLOGY OF BILHARZIA

The early lesions of bilharzia are due to the presence of the parasites and their ova in the tissues. The later lesions are due to disturbances of structure and function arising from the efforts of the body to throw off the infection and to repair the damage. Later lesions are also the result of bacterial invasion of devitalized tissues. The first clinical evidence of oviposition is passage of blood, which is caused by an inflammatory reaction in the mucosa either about the trigone in the bladder, or in the rectum, or in both. Soon there develop small areas of a sandy nature surrounded by hyperemia, or still more frequently the whole mucosa loses its normal bright appearance and becomes sandy (Fairley[4] and Madden[11]). The sandy appearance is due to clumps of ova lying in the tunica propria beneath the mucosa. The deposit of ova may extend until the mucosa looks like very fine sandpaper. In the bladder and ureters, urine salts are sometimes deposited on such a surface, giving rise to the foundation for a stone. Mucous membranes thus filled with ova are easily abraded and bleed readily. In order for the ova to escape

from the tissues, the mucosa must be broken through. Our studies show that this is accomplished by a process of ulceration. An intense inflammatory reaction occurs with the accumulation of many leucocytes, lymphocytes and endothelial cells. Among the leucocytes is a large number of eosinophiles. Irritation of the mucosa and the loss of its normal resistance to bacterial invasion result in actual abscess formation. The abscesses are as a rule very superficial. As they rupture into the lumen of the intestine or bladder, they discharge ova together with their contents. Granulations spring up at once in the ulcerated areas and may become excessive. As they grow they continue to carry ova up through the mucosa to the surface. From the fact that adult parasites are commonly found in the loose areolar tissue under such areas of ulceration and granulation tissue, and from the large numbers of ova in such a place, it seems likely that the gravid female is attracted to areas where the processes of tissue repair are active. The presence of bilharzia parasites and their ova seems to stimulate the tissue to activity.

The softer the mucous surface and the more glandular its epithelium, the easier it is for ova to pass through it. The columnar epithelium of the colon affords the easiest access to the outer world and ova are discharged in very large numbers through lesions in its surface. There is always excessive production of mucus, and in many areas the intestinal epithelium shows mucinous degeneration (Fig. 14).

The ova are aided in passing through the bladder mucosa by the distension and contraction of the organ, and by superficial ulceration. Abscess formation, such as is seen in the rectum, has not been noted in the bladder sections studied. In the cervical and vaginal mucosa it is more difficult for ova to escape from the tunica propria into the vagina. In our specimens small abscesses were seen to have formed around groups of ova. Small fistulae allowed the contents to escape into the vagina. Polyps are formed in the mucous membranes of the colon and the bladder. Their formation depends on the degree of infestation and on peculiarities in the reactivity of the host. They vary in size, and are often so large and numerous as to cause marked obstruction of the bowel. Specimens 3 to 4 cm. in diameter were commonly seen. The polyp may consist of a single lobule or it may be multilobular. The pedicle of the polyp may be very narrow and consist mostly of mucous membrane, in which case it is very friable;

or it may be broad and involve the deeper coats of the intestinal wall, in which case the polyp is likely to be very firm and fibrous. The lobules are covered with mucous membrane except for areas of ulceration where there is an abundant formation of granulation tissue.

In the Tanta cases polyps were found anywhere in the large intestine from the cecum to the anus, but were most often found in the descending colon, sigmoid and rectum. They occurred in a localized area or sometimes there was a diffuse polyposis of the whole intestine. In the bladder, polyps occurred less frequently than in the colon. They were located on the posterior wall near the trigone and were often associated with a malignant change. Very heavy infiltrations of the mucous membranes of the bladder and intestine sometimes occurred and resulted in a general thickening of their walls without the formation of polyps. In such a case the bladder had become a thick-walled non-contractile viscus with limited capacity and very septic walls. The sepsis is accentuated by the decomposition of blood and pus in the residual urine and a fatal issue is almost a certainty.

Microscopically the rectal polyp is seen to consist of a swollen, hyperplastic epithelium covering an irregular mass of connective tissue stroma. The epithelium is often broken by areas of granulation tissue and areas of mucinous degeneration of the goblet cells in the mucosa (Fig. 14). The stroma of the polyp is filled with bilharzia ova and in the vessels at its base there often are adult parasites of both sexes. If the polyp has been recently formed and is soft, a large number of polymorphonuclear cells, eosinophiles and lymphocytes are found in its stroma, and the ova appear undegenerated and intact (Fig. 6). If the polyp is older it is firmer, with a large amount of fibrous tissue in the stroma infiltrated chiefly with endothelial cells and lymphocytes (Fig. 11), and many of the ova are degenerate, the embryo is lost, and only the chitinous wall remains. The chitinous walls of ova are often surrounded by giant cells of the foreign body type and by pseudotubercles (Figs. 7 and 9).

Ova are much less frequently deposited under squamous epithelium than under either columnar or transitional epithelium. On the cervix, in the vagina and about the anus, however, such deposits are not uncommon. The ova are found in the corium and layers of the superficial fascia and are surrounded by an inflammatory reaction

and hyperplasia of the squamous cells. The result is a marked thickening and wrinkling of the surface. The papillae are hypertrophic and extend deeply into the corium. The epithelial thickening grossly resembles widespread confluent verrucae. Sections show the microscopic structure to be not unlike that of verrucae. As the thickening progresses, the tissues lose their vitality and small abscesses form about groups of ova in the corium. This is undoubtedly brought about by invasion of pus-forming bacteria. Abscesses form and the ulceration allows the offending ova to be discharged. The invaded area becomes very thick and edematous, with small and larger abscesses forming and rupturing on the surface. There is considerable production of granulation tissue and later of scar tissue. The epithelium becomes excessively thickened and rugose. Such a process, after it has continued for a long time, obliterates the normal structures. Cases are frequently seen in Egypt where the posterior and anterior culs-de-sac of the vagina are obliterated and the cervix is buried in a mass of scar tissue. The vagina itself may become constricted, causing more or less complete atresia.

Still less frequently ova are found deposited under the true skin. This occurs in the region of sinuses and other chronic inflammatory processes near the anus and about the genital orifices. Here, as under the moist squamous surfaces, there is no escape for the ova except through ulceration. Ova are not found in the epithelium but are seen closely related to the epithelial cells in an area of granulation or degeneration.

In all heavy infestations, ova are deposited in the muscular and serous coats as well as in the submucosa. Here the ova are in an abnormal situation and cannot escape from the tissues, so their life cycle cannot be completed. They are held prisoners, so to speak, in the tissues. The result is similar to that seen when other foreign bodies are deposited in the tissues. There is first an inflammatory reaction that is not suppurative. Large numbers of polymorphonuclear cells, lymphocytes and endothelial cells appear about the ova (Figs. 6, 8). Then, as the ova die, giant cells are seen (Figs. 7, 9). At times leucocytes and giant cells may be seen surrounding or actually within the ovum. Probably the leucocytes play a part in the removal of the embryo. The more resistant walls of the ovum remain unchanged or become calcified. Endothelial cells and lymphocytes become grouped about them and finally they are walled

off by dense fibrous tissue (Figs. 10, 11). These are the pseudotubercles very commonly seen in bilharzia tissue.

Grossly the tissue becomes hard and fibrous, cuts with a gritty feel, and presents a sandy appearance.

The peritoneum may be thickly studded with tubercles, usually distributed most abundantly throughout the lower abdomen and over the colon. These hard nodules varied in size in the specimens studied from those that could be scarcely seen by the naked eye to masses of tumor-like structure the size of a fetal head. The large masses involved all the walls of the intestine and the surrounding tissues, all being matted together in an inseparable mass. Some sections of severely involved intestines looked grossly like tumors, but microscopically showed only massive infiltration with ova, pseudotubercle formation, and excessive formation of fibrous tissue. The pseudotubercles did not show caseous necrosis.

In the interlobular veins of the liver the presence of the parasites and possibly products liberated by them causes, first, a marked enlargement, and later a peculiar periportal fibrosis, described as a pipestem cirrhosis (Symmers[18]). In young children and young adults, the liver extends down to the umbilicus and fills the whole upper right quadrant of the abdomen. In later life and in older patients the liver is smaller and nodular. Grossly it is coarsely lobular and very firm. It cuts with very much increased resistance, and throughout its substance are very marked bands and cords of fibrous tissue about the portal spaces. Dew [3] describes all grades of tissue change in the liver from a mild generalized fibrosis with hepatic enlargement such as is seen in earlier and milder cases and especially in connection with *S. hematobium* infections, to the severe periportal cirrhosis seen in later severe infections with *S. mansoni*. The specimens examined in this study were of the severe type and the periportal cirrhosis was very marked. All of these cases were heavily infested with *S. mansoni* parasites and showed pronounced intestinal involvement.

Microscopically the portal spaces showed a decided proliferation and tortuosity of the bile ducts. The veins were dilated and contained parasites. There was a great increase of the fibrous tissue which contained large numbers of lateral spined ova. In one case examined, the cords of fibrous tissue surrounding the portal spaces were two to three centimeters in diameter. Contraction of these

bands had resulted in compression of the liver parenchyma and reduction in the size of the organ. The liver cells were atrophic, due to compression, and endothelial cells contained a brown pigment.

Splenic enlargement is commonly, but not constantly, associated with bilharzia infection. It is apparently most common in *S. mansoni* infections. The average weight of the spleen in five cases at Tanta where the spleen was removed surgically was 1168 gm. The organs were firm and uniform in consistence, cut with increased resistance, and presented a pulp that did not scrape away readily. Microscopically there was evident increase in the amount of fibrous tissue. The follicles and trabeculae were widely separated and the splenic pulp was very cellular and fibrous. No parasites or ova were seen. The cells were mainly of the endothelial type and contained a brown pigment that was similar in nature to that found in the enteric canal of the bilharzia parasite (Manson-Bahr[1]), and in the endothelial cells of the liver.

In severe infestations ova are found deposited in all abdominal organs. In this study they have been found in the walls of the small intestine, appendix, cecum and colon; in the pancreas, liver, retroperitoneal lymph nodes and omentum; in all points of the peritoneum, particularly over the colon, bladder, and in the sacs of inguinal herniae; in the ureters, bladder, seminal vesicles, epididymis, testes, ovary, uterus, cervix and vagina. Ova have been discovered in the lungs, brain and kidneys.

The later complications of bilharziasis are those that often cause the greatest debility and bring about a fatal issue. In itself bilharzia is not likely to be a lethal disease. The most frequent complications occur in the urinary system. One of the early manifestations of bilharzia infection is swelling about the ureteral openings into the bladder. Stasis in the ureters and kidneys follows. Bleeding into the bladder and ulceration of its mucosa sooner or later results in cystitis. Long-continued irritation of the bladder wall causes thickening and loss of elasticity. Residual urine and blood in the bladder result in still further sepsis. Ascending pyelitis and pyonephrosis are very common sequels. Deposits of urine salts occur and stones are formed in kidney, ureter and bladder.

Inflammation about the trigone and urethra causes swelling and later strictures which interfere with emptying the bladder. Abscesses form about the trigone and in the prostate. Extravasation

of urine occurs and abscesses and later sinuses form in the perineum and scrotum. Frequently cases were seen where extravasation caused the scrotum to slough away, leaving the testes exposed. In one case the extravasation extended up in the abdominal wall as high as the umbilicus, resulting in severe sepsis and death.

About the anus and rectum, abscesses and sinuses are common. Stricture of the rectum is frequent as the result of trauma to the walls of the gut. Polyps in the intestines cause the patient to go to stool constantly, and the straining results in relaxation of the perineal muscles, edema of the gut and prolapse of the intestines. As much as eight inches of the lower bowel have been seen protruding from a patient after he has been at stool. One of the specimens studied was from such a case. Constant straining during his illness had caused marked prolapse of the lower bowel. A conical mass of swollen, ulcerated, everted intestine protruded from the anus, which was much dilated. After death the bowel was removed. The lumen was found to contain bilharzial polyps. The mucosa was very much inflamed, in areas ulcerated, and contained large numbers of ova. The walls of the intestine and the surrounding fascial supports were edematous and contained bilharzia ova and an inflammatory exudate.

Ileus is common, due to adhesions about the intestine or to actual narrowing of its lumen by fibrosis or by polyps.

Abscess formation in the liver or abdomen has not been noted. Bilharzial appendices sometimes become septic and are difficult to treat surgically because of the low resistance of the surrounding tissue.

Thrombosis of the veins is common. It may occur in the mesenteric veins and cause an ileus and gangrene of the gut. Cases were seen in which the femoral vessels, abdominal vena cava and portal vessels were involved. In one specimen studied there was extensive mesenteric thrombosis and thrombosis of all branches of the portal veins in the liver. The vessels contained large numbers of parasites.

In our experience the blood in bilharziasis shows anemia that is out of proportion to the blood losses from the bladder and bowel. In cases of average severity the hemoglobin ranges between 30 per cent and 45 per cent, the red count from less than one million to three million. The white count is usually about 10,000 to 12,000 and there is a marked eosinophilia. Day,[2] in his report on the blood

changes in bilharziasis, selected early and uncomplicated cases and concluded that bilharziasis *per se* produces only slight anemia, and the most characteristic change is eosinophilia.

Tumors are commonly seen associated with bilharzial tissues. Ferguson,[6] and Madden,[11] call attention to the tumors of the bladder and say that both sarcoma and carcinoma occur. True carcinoma of the bladder has frequently been seen during this study and in at least two instances tumors that look very much like sarcomas were found in the bladder.

In the colon and rectum two examples of mucinous carcinoma were seen, one in the appendix and the other in the rectum.

Discussion

The study of this material was undertaken in the hope that the character of the pathologic processes resulting from the presence of bilharzia parasites and their ova in the tissues might be more clearly understood. The following points have been more clearly brought out.

1. It has been recognized that the presence of the parasites and their ova in the tissues is attended by a primary inflammatory reaction of a nonsuppurative nature. We wish to point out that whether this inflammation is followed by ulceration or fibrosis depends on the location of the deposition of ova. We believe that there is no inherent quality in the parasites or the ova that is sufficient, of itself, to produce ulceration. The ulcerative process seems to be dependent on the action of secondary bacterial invaders on tissues of diminished vitality. Where the tissues are not exposed to such invasion as, for example, in the peritoneum, omentum and deep tissues like muscle, abscess formation and the discharge of the ova do not commonly occur. Where they do occur, the process begins with suppuration in more superficial tissues. In superficial tissues near the epithelial lining of a hollow viscus or even under the skin, the primary inflammation is followed by ulceration and discharge of the ova.

In the deeper tissues and in the abdominal organs such as the liver, abscess formation has not been seen. The ova, at first surrounded by inflammatory cells, become isolated by fibroblasts and giant cells of the foreign body type. The ultimate result is the formation of a granuloma, the characteristic unit of which is the bil-

harzial pseudotubercle. The excessive fibrosis often resulting late in such a process produces marked distortion or even obliteration of structures, interferes with physiologic function and is the basis of many of the serious complications occurring late in the disease.

2. That the bilharzia parasite produces nocuous substances in the body of its host is evident on the basis of clinical experience with patients who have acquired a severe infection in a short period of time, and from experimental evidence (Fairley[5]), from animals infested with large numbers of cercariae. Experimental animals heavily infested die before oviposition occurs.

The nature of this nocuous substance is not clearly established but the following facts are noted in evidence that it is the result of simple protein splitting rather than toxin production:

(*a*) Histologically there is abundant evidence of the digestion and removal of the embryos by the phagocytic cells of the body. This is attended by blood changes that are characterized by a mild to severe anemia of the secondary type, slight leucocytosis and a marked relative increase in the number of eosinophiles and large mononuclear cells (personal observation, and Day[2]).

(*b*) Much pigment similar to that deposited in malarial infections is deposited in the internal organs, particularly the spleen and liver. This pigment is similar in character to that seen in the enteric canal of the parasites.

(*c*) Fairley has shown that there is a specific reaction in the body that results in a constant (88 per cent) fixation of complement when extracts of the livers of infected snails are used as the antigen.

(*d*) Clinical experience does not indicate the formation of immunity in the patient even after he has been long infected.

Grateful acknowledgment is made of the help and advice given by Professor H. T. Karsner and Professor Harry Goldblatt of Western Reserve University; and Doctor Otto Saphir of the Cleveland City Hospital. The photomicrographs were made by Professor Karsner.

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DESCRIPTION OF PLATES

Plate 1

Fig. 1. Bilharzia parasite, male, in an interlobular vein of the liver. Note the large size of the vessel and the surrounding fibrous tissue.

Fig. 2. Bilharzia parasites, male and female, in the veins at the base of a rectal polyp. The male enfolds the female.

1

2

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Plate 2

Fig. 3. Bilharzia parasites, male and female; the cross-section taken posterior to the bifurcation of the intestinal canal of the male.

Fig. 4. Bilharzia parasites, male and female, in cross-section through the ovary of the female.

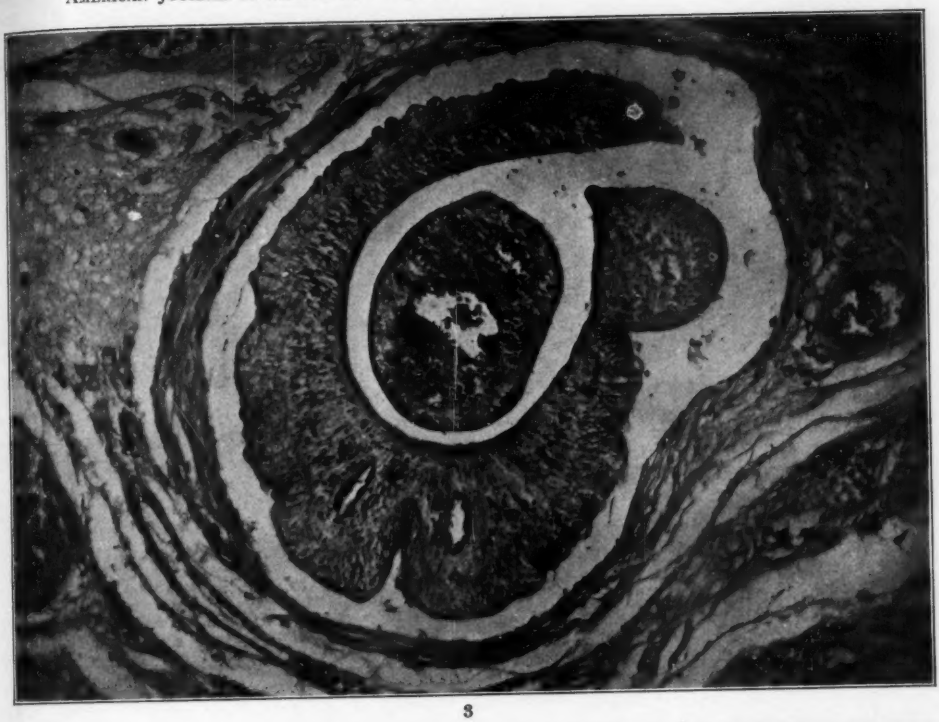

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PLATE 3

FIG. 5. Bilharzia parasites, male and female. The females are not in the gynecaproic canal of the male.

FIG. 6. Bilharzia ovum, *S. mansoni*, from a rectal polyp, showing the surrounding inflammatory reaction. Many of the polymorphonuclear cells are eosinophiles.

FIG. 7. Bilharzia ovum, *S. mansoni*, in a rectal polyp. This ovum is dead and a giant cell has formed against its shell and within its lumen.

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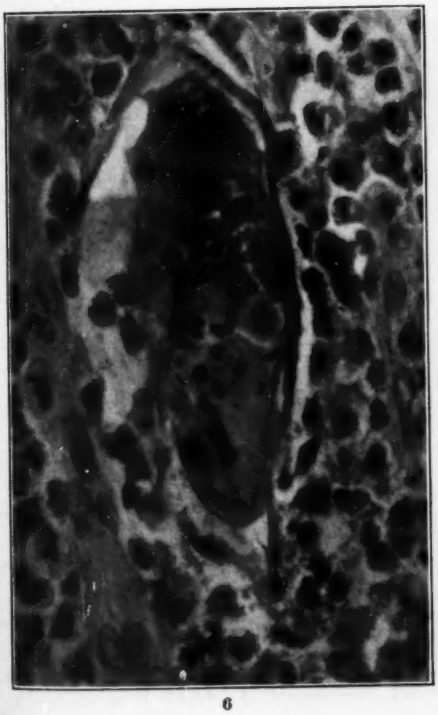

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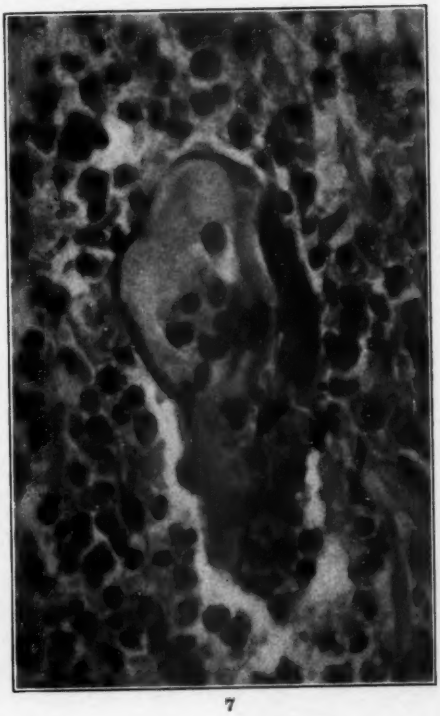

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Hutchison

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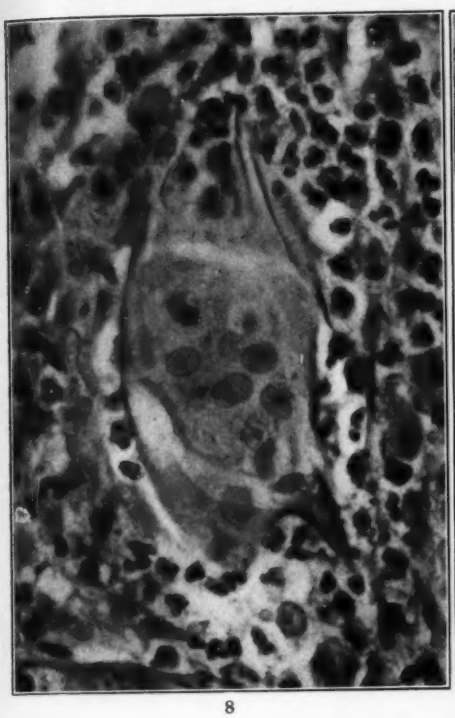
PLATE 4

FIG. 8. Bilharzia ovum, *S. mansoni*, showing the lateral spine. The embryo is replaced by tissue cells.

FIG. 9. A very large giant cell about an empty ovum.

FIG. 10. Pseudotubercles about ova in the fat of an epiploic appendage.



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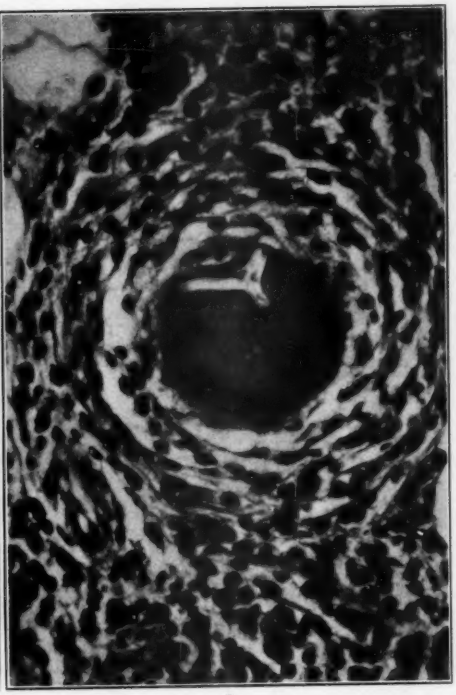

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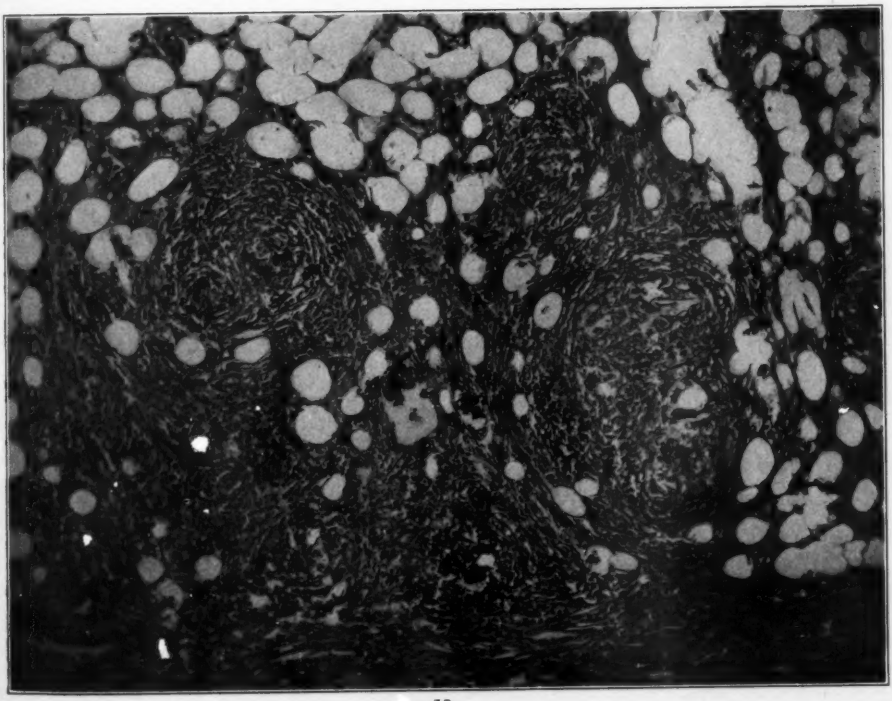

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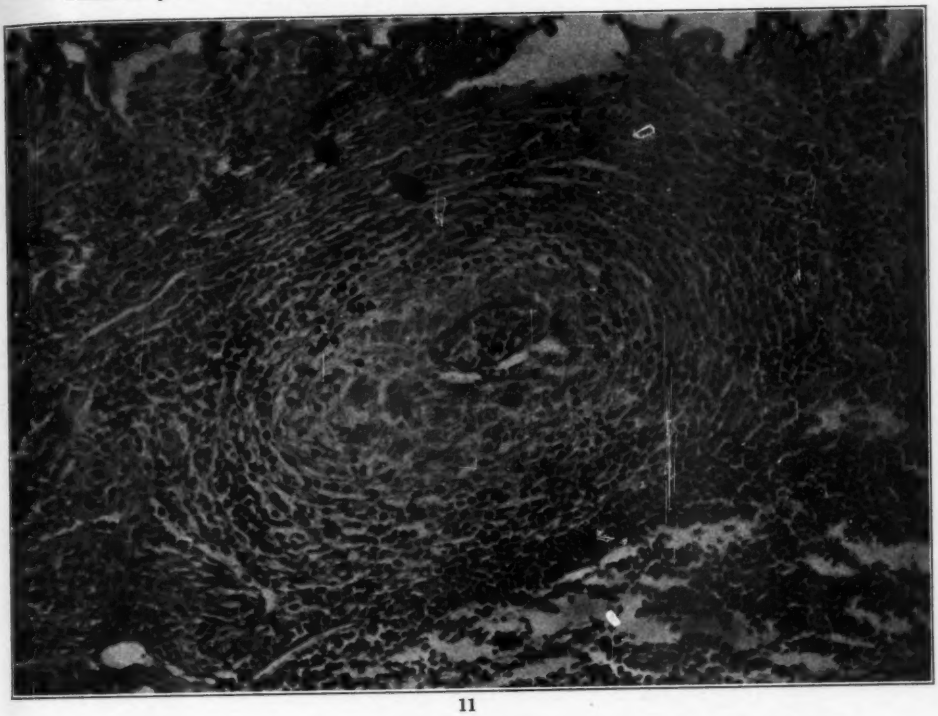
PLATE 5

FIG. 11. Pseudotubercle, late stage, with marked formation of fibrous tissue.

FIG. 12. Bladder wall showing dense infiltration with ova of *S. hematobium*, many of which are calcified.



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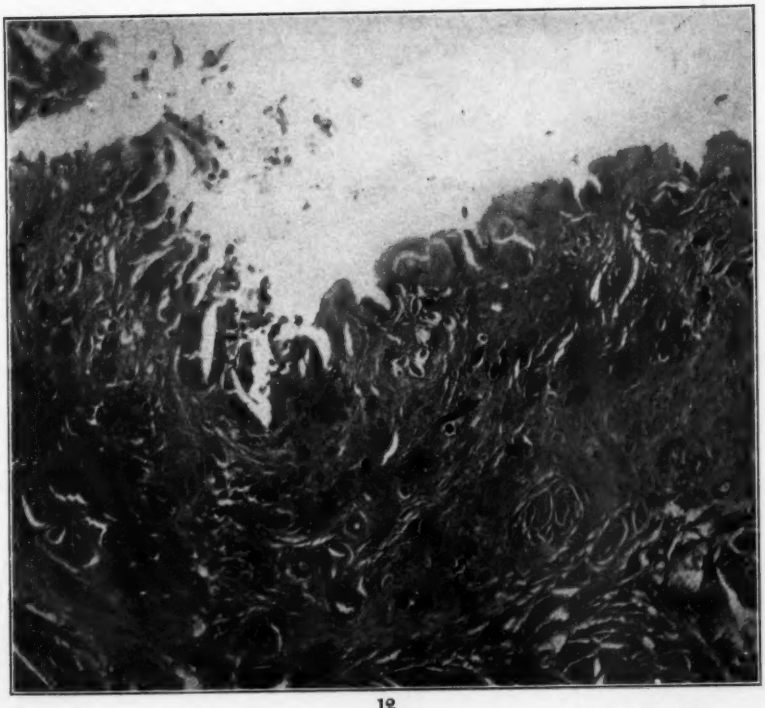

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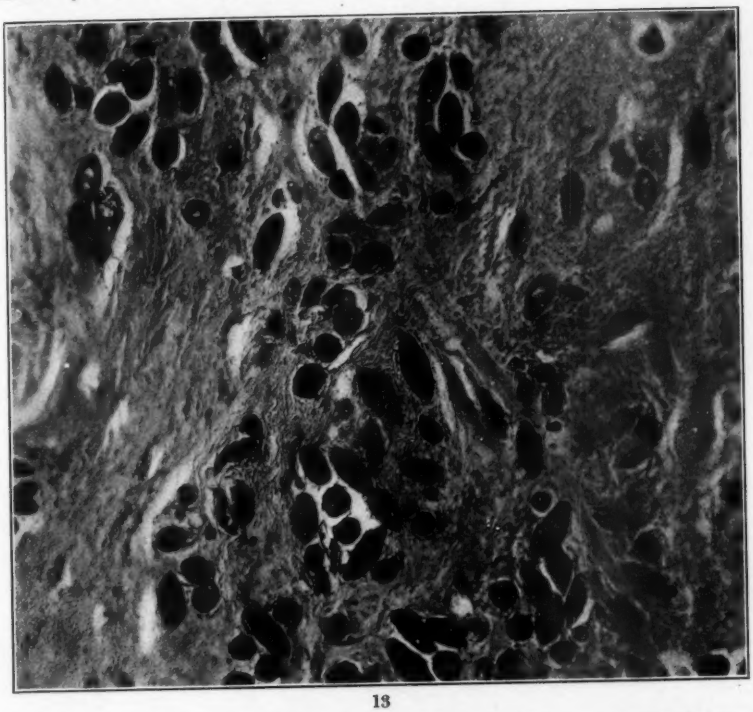
Hutchison Pathology of Bilharziasis

Plate 6

Fig. 13. Terminal spined ova of *S. hematobium* in the bladder wall, (comparatively low magnification).

Fig. 14. Mucinous degeneration in the columnar epithelium on a rectal polyp. The dark spot under the mucosa is the cross-section of an ovum.



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Hutchison Pathology of Bilharziasis

A STUDY OF THE CIRCULATION IN THE NORMAL AND PATHOLOGIC KIDNEY WITH ROENTGENOGRAPHIC VISUALIZATION OF THE ARTERIAL TREE, INCLUDING THE GLOMERULI *

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INTRODUCTION

Our knowledge of the structure and physiology of the kidney has steadily progressed in recent years, but the methods employed by the workers in these fields have not been adopted quite so vigorously by the student of general pathologic conditions of the kidney.

Oertel [1] in 1910 maintained that in order to establish a pathologic physiology of the kidney it would be necessary to "construe the plan of the whole pathological organ." Not until the recent work of Traut,[2] however, has it been possible to interpret accurately the plan of the kidney from an anatomic standpoint, and this investigator is convinced that the unit structure of the kidney is largely explainable on the basis of a unit blood supply. It would seem therefore that a study of a series of kidneys from necropsy material by some method which clearly, accurately and completely visualizes the arterial tree, might offer a valuable contribution toward our conception of renal pathology and its relationship to functional capacity.

HISTORICAL

Studies of the renal vascular tree have been made by numerous workers using celloidin and corrosion methods, but with such a procedure one is handicapped from a pathologic standpoint by the unavoidable destruction of the kidney tissue.

The use of a radiopaque injection mass for the study of the circulation dates back almost as far as the use of the Roentgen rays for diagnostic purposes. The earliest investigations are credited to V. Dutto, an Italian, who in 1896 employed in his studies a suspension of calcium sulphate in water. Since that time a large number of substances have been tried by different investigators for this purpose, a concise résumé of which is given by Gough.[3]

* Received for publication August 15, 1927.

In the study of the circulation of the kidney by these methods the earliest comprehensive work appears in 1913 by Hauch [4] who used a suspension of red lead oxide in paraffin oil. By this means he obtained beautiful and accurate radiographic reproductions of the arterial tree. He mentions the fact that glomeruli were injected, but these are lost in the reproductions accompanying his article, the injection not extending beyond the interlobular arteries. Although he demonstrated moderate and severe degrees of renal arteriosclerosis, yet his study was preliminary in character as he gave particular attention to the method and no conclusions were drawn from a pathologic standpoint.

In 1917 and 1918 Gross,[5] using gelatin preparations of Prussian blue and carmin, made a roentgenographic study of normal and arteriosclerotic kidneys with a gelatin barium sulphate injection mass. This preparation gave a clear-cut reproduction of the arterial tree extending through but not beyond the interlobular branches. More recently Hinman, Morison and Lee-Brown [6,7] used a thin suspension of barium sulphate in a 50 per cent aqueous solution of sodium bromide to demonstrate this portion of the vascular tree, but found the particles in the mass too large to go beyond the interlobular arteries. For demonstration of the afferent and efferent glomerular circulation they substituted a celloidin corrosion method with excellent results. This latter method while admirably adapted to an anatomic study is less adaptable to pathologic work, not only because of the delicate, time-consuming procedure, but also in that it destroys the tissue and precludes histologic examination.

Method

For our purpose a radiopaque mass developed by Hill [8,9] in 1921, published by him in 1924 and completed in 1927, appeared most suitable. As prepared by him, the preparation for general use consists of a 17 per cent suspension of bismuth oxychloride (a special brand) in water containing 10 per cent acacia. A number of preliminary tests with this material indicated that a preparation of 25 per cent bismuth with 12 per cent acacia visualized both the large vessels and glomeruli more satisfactorily. A microscopic study of the individual particles in the suspension as prepared in this manner showed them to be quite uniform in size and shape, measuring

from 0.5 to 3 microns; however, these particles tend to become loosely held together, appearing as irregular masses varying from 6 to 60 microns. The larger of these apparent clumps might well be expected to obstruct branches of relatively large vessels causing artefacts, but neither microscopic kidney sections (Figs. 2, 3, 4) nor magnification of the roentgenograms indicated any such condition.

A more detailed report as to the preparation and technic is deemed unnecessary and undesirable because of the simultaneous publication by Hill of the entire method [9]; particularly as the percentages of bismuth oxychloride and acacia given above apply to renal studies and would occasion difficulties if applied to other circulatory research.

Pathologic Material: The study was made on a series of forty-eight kidneys obtained from the routine necropsies performed at the Pennsylvania Hospital during the winter and spring of 1927. As a rule the right kidney was chosen and after injection was preserved for further gross or histologic examination.

Technic: It seemed desirable that the procedure should be as simple as possible and without elaborate apparatus, so as to be applicable to the exigencies of the necropsy room. After a few trial injections with the organ *in situ*, this method was abandoned and the following procedure was adopted. The renal artery was cut at the aortic junction and the kidney was then removed in each case with the surrounding perirenal fat and the adjacent suprarenal gland. The organ was immediately placed in the ice-box in physiologic saline solution until an opportunity for injection was afforded. In this way kidneys were injected for the most part a few hours after death, but in some cases a longer time elapsed. In one instance a kidney was kept in this manner for about eight days and to our surprise the prolonged delay did not seem to affect the subsequent study. When ready to inject, the organ was brought to room temperature and the renal artery was ligated under saline, any air thus being excluded from the vessels. The injection mass was introduced into the renal artery with a 20 cc. syringe and hypodermic needle, using gentle digital pressure. Leaking vessels were caught with hemostats when necessary. By placing the tissue immediately in saline, the air is not only excluded from the vessels but injection into the saline-filled system dilutes the first part of the suspension, so that the same effect is produced as if a thin suspension was fol-

lowed by a heavier one. It is felt that the cold saline also probably prevents the formation of clots and possibly helps to dissolve them.

The injection was carried out carefully and slowly, requiring from five to twenty minutes. It was considered complete when there was an even distribution of tiny white points visible through the kidney capsule. In several injections just as the procedure was completed the return venous flow of blood showed a white tinge of the injection mass, but in no instance was a sufficient quantity of the mass passed through the capillaries to visualize the veins. Where infarcts or cortical scars were present these areas refused to fill out either with prolonged gentle pressure or greater pressure. The fatty renal fascia was then stripped off, any leaking points clamped and tied if necessary, and any injection material on the surface washed off carefully in cold water and the organ dried with a towel. Stereoscopic roentgenograms were taken as soon as convenient using a low milliamperage and low spark gap technic. In a few instances where the injected specimen was not roentgenographed for eight to fifteen hours after injection, the settling out in the larger vessels produced artefacts.

The amount of material injected proved to be fairly constant (where leakage was negligible) ranging from 7 to 18 cc., and averaging from 12 to 15 cc.; kidneys of children and contracted kidneys taking a smaller amount, and large kidneys, especially those with passive congestion, taking a larger quantity.

Results

General: Roentgenograms of the injected kidneys gave a clear-cut reproduction of the arterial tree including the glomeruli, coinciding accurately with the present conception of its anatomy so clearly presented by Lee-Brown.[7] In a single instance, which will be discussed later, the pyramidal vessels were injected (Fig. 10). In each instance the films were studied both stereoscopically and separately with a hand lens. Stereoscopic examination proved to be of particular value in the study of the coarser vascular tree, the pyramids appearing as well defined hollows, between which the interlobar branches could be easily traced with the arcuate arteries arching over their bases. The relationship of areas of infarction, scars, metastatic nodules, tubercles, and artefacts was also best under-

stood by stereoscopic examination. The finer vessels were studied to best advantage with a hand lens although even with the naked eye the straight, almost parallel interlobular arteries could be readily seen surrounded by compact areas consisting of many tiny points representing the glomeruli (Fig. 8).

For further description of the findings, the cases are divided into the following groups: I. *Normal arterial tree;* II. *Arteriosclerosis* (those two groups have been based primarily on the roentgenographic appearance); III. *Thrombosis, infarction and metastatic tumors;* IV. *Syphilis;* V. *Tuberculosis;* and VI. *Hydro- or pyonephrosis.* Group I includes eighteen cases in which no pathologic change was demonstrable in the arterial tree. Group II is composed of seventeen cases in which there was some degree of generalized arteriosclerosis. Group III consists of six cases showing thrombi or infarcts in the kidney and one case in which there were multiple metastatic tumor nodules. Group IV includes six cases of syphilis, which are considered separately because of the often discussed question as to whether changes in the small vessels in such cases are of syphilitic origin or merely represent simple arteriosclerosis. Group V includes four cases of generalized miliary tuberculosis. Group IV is composed of four cases of hydro- or pyonephrosis which were encountered in the series.

GROUP I. *Normal Arterial Tree.* In the normal arterial tree the primary division of the renal artery appears on the film either just within or lying closely outside the edge of the cortex at the hilum. The vessels show a uniform gradual diminution in the size of their lumina as they progress from the hilum toward the cortex. Except for the primary branches arising from the renal artery the branches come off at an acute angle. The interlobar and arcuate branches, passing up between the pyramids, spread out in graceful curves and arches over the bases of the pyramids not unlike the architecture of a great elm tree (Figs. 5, 6, 7 and 8). The interlobular arteries are slender, delicate, of uniform size, very straight, almost parallel and give rise to a picture of a uniformly thick vascular cortex. The glomeruli are very fine, numerous and uniform in size. They are grouped closely around the interlobular arteries giving the effect stereoscopically of slightly cone-shaped columns with the interlobular artery in the center and their bases toward the periphery of the cortex (Fig. 13).

It is of interest to note the variety of pathologic conditions in which injection showed a normal arterial tree. To establish our conception of the normal, particular attention was given to cases in which the age of the individual was within the first three decades of life. Of two in the third decade, one, age 24, died of generalized melanomatosis (Fig. 13); the other age 27, died of vegetative endocarditis (Fig. 8) and will be referred to again in a later group. Two cases of rheumatic fever are representative of the second decade, one in the acute (Fig. 5) and one in the chronic stage. The patients in both of these cases were 14 years of age. A single case of a patient 8 years of age, who died of extensive burns of the body, represents the first decade (Fig. 7). Cases showing infarcts, thrombi, or metastatic tumor nodules are included in Groups I or II depending on the appearance of the arterial tree on the films.

With kidneys from individuals in mid-life the incidence of demonstrable vascular disease is so high that selection of cases is more difficult. Five cases were listed as normal in which the ages vary from 40 to 51 years, and in which there were no appreciable arterial or arteriolar changes microscopically. On the roentgenograms the arterial tree appears somewhat less delicate than in the series of younger individuals. The glomeruli appear to be of approximately the same size and number, and the cortex of the same width, but the arcuate and interlobar branches show more abrupt changes in size of the lumina while the curves and arches lose some of their gracile, slender form (Fig. 6).

Among the conditions in which a normal vascular tree was visualized were three cases of malignant tumor, a variety of infectious conditions and one case of subacute nephritis (Fig. 9). In this series we are confronted with various degrees of passive congestion and cloudy swelling in the kidney, with one case presenting an active nephritis. To our surprise none of these factors appeared to influence or to limit the completeness of the injection. Figure 5 shows a kidney with marked passive congestion from a case of cardiac failure in active rheumatic fever. The injection is heavy, uniform, and the injection mass is beginning to enter the pyramidal vessels. Figures 9 and 14 show a roentgenogram of a kidney which histologically showed not only swelling of the tubular epithelium but also an active nephritis. Grossly this kidney was a typical example of subacute nephritis or so-called "large white kidney," yet the injection

visualizes a beautifully delicate vascular tree and from the roentgenogram it would be impossible to say that a lesion existed in this kidney.

Figure 10 is the roentgenogram of the one case in the entire series in which an injection of the pyramidal vessels is obtained which approximates completeness although some degree of pyramidal injection was obtained in several instances. The reason for this is somewhat obscure since the same technic was used. The case was one of gangrenous endometritis following an abortion, in a woman 33 years of age, who presented a profound anemia together with evidences of severe toxemia. At necropsy there was a severe toxic hepatitis and the kidneys showed marked cloudy swelling and passive congestion. The blood urea nitrogen (postmortem) was not, however, increased. The possibility presents itself that the vessels were unusually deficient in tone due to the toxic phenomena and therefore permitted a more complete penetration of the injection mass into the finer vascular tree. The pyramidal arterioles are very straight, but wide and feathery converging toward the tip of the pyramid. From the base of each pyramid delicate vessels can be distinguished running up into the cortico-medullary zone which are very tiny but not as straight as the interlobular arteries among which they lie (Fig. 15).

GROUP II. *Arteriosclerosis.* The changes in the coarser portion of the vascular tree have been visualized by Hauch and later by Gross, the latter tabulating them in detail. In the advanced stages of arteriosclerosis of the kidney associated with a generalized contraction of the entire organ the changes are most striking. The lumina, especially those of the larger vessels, are of very uneven caliber presenting many constrictions and irregularities due either to plaques in the intima or thickening of the walls, while adjacent areas show either real or apparent dilatation. The branches tend to arise more nearly at a right angle. The interlobar and arcuate arteries are wider, and instead of tapering gradually toward the cortex maintain a rather large caliber and end abruptly in smaller branches. The normal curves have become angular, and the vessels tortuous in their course. The interlobular arteries are fewer, shorter, and run less directly to the cortex, and in severe cases even exhibit a tortuous course (Fig. 11). The glomeruli are fewer in number, considerably enlarged and are seen clumped around areas of the richest

surviving vascular supply (Figs. 11 and 16). The entire picture of the arterial tree is that of a gnarled, dead oak, rather than the graceful architecture of the spreading elm tree. As the kidney contracts it shrinks uniformly but the coarser arterial tree maintains the same size and position, so that there is the appearance of a drawing out of the renal artery and its larger branches from the hilum.

In the milder degrees of nephrosclerosis the earliest change seen in the roentgenograms appears in the arcuate and peripheral portions of the interlobar arteries. These appear coarser and run a tortuous course (Fig. 12). In this stage the glomeruli may show no demonstrable change (Fig. 17) although in several instances small cortical defects appeared in the roentgenograms. On microscopic examination these were found to consist of scarred areas lying beneath the capsule. Histologically the vessels showed arteriolar sclerosis.

Between this and the contracted kidney first described there are varying degrees of arterial change. In all, however, the degree of change in the interlobar and arcuate arteries is a striking feature. Changes in the size and number of functioning glomeruli bear a close relationship to the condition of these vessels as seen in the picture of the arterial tree.

This series includes kidneys from sixteen cases ranging in age from 33 to 77 years. Only one case, however, was under 40 years, and half were over 50 years of age. In all except two cases, generalized arteriosclerosis was an important factor in the anatomic diagnosis and these two cases showed only mild arteriolar and arterial change in the kidneys.

Differentiation between nephritis of arteriosclerotic origin and other types of nephritis. In connection with the studies on kidneys showing advanced degrees of arteriosclerosis, it has seemed particularly interesting to determine whether this method of visualization of the vascular tree would prove of value in the differentiation between the contracted kidneys of arteriosclerotic origin (nephrosclerosis) and the contracted kidneys of essentially toxic or bacterial origin (chronic glomerulonephritis). A single specimen representing the latter type of lesion was available for this comparative study. No attempt has been made to define the picture of chronic glomerulonephritis on the basis of this isolated case but the findings are sufficiently striking to warrant their presentation. The case was that of a male negro,

44 years of age, who gave a history of failing renal function for a period of at least nine years. At necropsy the kidneys presented the picture of chronic glomerulonephritis associated with a relatively mild degree of vascular sclerosis. The roentgenogram (Fig. 18) is in contrast to that of the arteriosclerotic kidney (*cf.* Figs. 11, 16).

It will be noted that sclerotic changes in the arterial tree are of moderate degree and occur largely in the arcuate arteries. The cortex, although twice as wide as in the case of nephrosclerosis, shows only a very few, large and fairly evenly distributed, glomeruli. Interlobular vessels where distinguishable are thick and tortuous, and an almost complete injection of the pyramidal vessels is evident. This last feature appears especially remarkable in view of the apparent distortion of the normal circulation.

GROUP III. *Thrombosis, Infarction and Metastases.* This group includes seven cases; one with metastatic tumor nodules, two with thrombi, and four with infarcts. On the roentgenograms of kidneys with the arterial tree injected, infarcts and thrombosed vessels cause a ragged, irregular defect, extending down from the cortex corresponding quite accurately in size to that of the gross lesion. Metastatic tumor nodules are frequently well rounded, sometimes raised above the surface, and appear also as defects in the injection of the arterial tree. It must be remembered that scars, tubercles, and artefacts may give the appearance of thrombosis or infarction, whereas retention cysts and abscesses simulate the picture of metastatic nodules, so that a careful check by gross and microscopic study of the kidney is essential. However, the injection method appears to be of very definite value for the detection of certain lesions of this type and in our hands has, in two instances, enabled us to demonstrate recent infarction where it was impossible on gross examination of the organ to distinguish any change in the tissue in the thrombosed area and hence there was no indication for histologic study of the particular area except the defect in the roentgenograms. In three cases white infarcts were readily seen on gross examination, and the appearance of these on the roentgenograms was essentially the same as those in the cases showing earlier lesions except that the areas of infarction were somewhat less extensive (Figs. 7 and 8).

One case in which there was a small aneurysm of the abdominal aorta at the level of the renal arteries is of special interest. The right kidney was very large while the left was about one third the

size of the right and had a peculiar bulb-like enlargement of the lower pole which was supplied by a separate anomalous artery arising from the aorta. The left main renal artery was occluded by a laminated thrombus for a distance of two and a half cm. from the aorta, distal to which it was collapsed and flabby. Both kidneys were injected for roentgenography (Fig. 19). The right showed slight sclerosis of the interlobar and arcuate arteries. In the left, the lower pole was similar in appearance to the right kidney, but the upper two thirds of shrunken kidney showed small vessels, the branches tending to be drawn out at the hilum and more parallel than normal. The arcuate vessels were tortuous, almost spiral, yet without the marked clubbing of severe arteriosclerosis. The cortex was but 1 to 2 mm. in width and the glomeruli were not injected. During the injection it was noticed that a small amount of the suspension came through into the renal pelvis, which would suggest tiny breaks in the severely damaged tissue and this is further borne out by the fact that the patient had had hematuria before death. The perforating capsular arteries were remarkably large and the possibility of a very deficient anastomotic blood supply by this route is to be considered (Belt and Joelson [15]). The picture is evidently the result of a relatively slow occlusion of the blood supply rather than a sudden blocking of the renal artery, and stands in sharp contrast to the cases of sudden blocking of a vessel with subsequent death of the tissue in the area supplied by it.

Group IV. *Vascular Syphilis.* This series includes six cases, all of which exhibited syphilitic aortitis and four of which presented aortic aneurysms. Two cases, which showed aneurysms of the aorta, displayed a normal arterial tree both on roentgenograms of the injected specimens and upon gross and histologic examination. The ages of these cases were 31 and 50 years. Three cases exhibited sclerotic changes in the interlobar and arcuate arteries and their branches. The ages here ranged from 52 to 64 years. In the remaining case cerebrospinal syphilis was a prominent feature. The kidney of this patient showed marked hydronephrosis and pyelonephritis. The changes in the roentgenograms here, consisting chiefly of an elongation of the primary branches of the renal artery and the interlobar arteries with slight enlargement of the arcuate branches, were essentially those produced by hydronephrosis which have been described by Lim [10] and again by Hinman and Morison.[11]

It is impossible to draw conclusions from so small a series as to whether the high incidence of arteriosclerotic change in the renal vessels in this group is due to the common association of syphilis with simple arteriosclerosis of the medium-sized and small arteries as emphasized by Warthin,[12] or whether the fact may be accounted for by the advanced age of these patients. It is worthy of note, however, that the roentgenographic appearance of the changes in the arterial tree is similar in all respects to those noted in the series of arteriosclerotic cases. Histologically the picture is also essentially that of arteriosclerosis although in one case moderate obliterative endarteritis was present.

GROUP V. *Tuberculosis.* Out of the four cases of generalized miliary tuberculosis in the series, tuberculous lesions were found in the kidneys in only three instances. The striking feature here was the resemblance between the defects produced by tuberculous lesions and those produced by thrombi and infarcts. We were unable to distinguish the presence of tubercles in roentgenograms of injected kidneys until they reached a size of about 1 to 2 mm. in diameter and the picture then was that of tiny or small defects, apparently the result of encroachment of the spreading tubercle on surrounding capillaries, glomeruli, and arterioles. The appearance was characteristic only in respect to the widespread distribution of tiny defects, all of which were of approximately the same size. Later, when the tubercles became confluent, they appeared more as small infarcts or scars, although possibly more superficial and less likely to involve small arteries.

GROUP VI. *Hydronephrosis.* There were also four cases of hydro- or pyonephrosis encountered in the series, only one of which was of marked degree. Subsequent to injection of the arterial tree, a pyelogram was made in each of these cases, but the changes noted were constantly proximal to the interlobular arteries and the findings add nothing to the work already done on this subject (Lim,[10] and Hinman and Morison [11]).

RELATIONSHIP OF DEMONSTRABLE VASCULAR CHANGES TO KIDNEY FUNCTION

An estimate of the functional impairment of the kidneys in this series is available in thirty-one cases in which terminal urea nitrogen and creatinine determinations were made on the blood. Except in

three instances these determinations were done postmortem on blood obtained at necropsy, as it has been shown that such data are reasonably accurate within a small percentage of error when the blood specimen has been taken within twenty-four hours after death (Paul [13]).

The cases in which blood urea nitrogen determinations are available are fairly evenly distributed throughout the groups (Table I).

TABLE I

Showing the Percentage of Cases with High and Low Blood Nitrogen Figures in each Group

Group	Total cases	Number of cases with urea nitrogen and creatinine determination on blood	Cases with normal blood urea nitrogen		Cases with high blood urea nitrogen	
			Number	Per cent	Number	Per cent
I. Normal	18	9	3	33	6	66
II. Arteriosclerosis	17	14	4	28	10	71
III. Infarcts	7	4	0	0	4	100
IV. Syphilis	8	5	1	20	4	80
V. Tuberculosis	4	4	2	50	2	50

In the two larger groups (I and II) it is surprising to find that the percentage of cases showing a high blood urea nitrogen is almost as great in the group of so-called normals as in the arteriosclerotic series. Moreover, if we exclude from the later group one case of severely contracted kidney in which there was an active nephritis at death, and from Group I the case of subacute nephritis, it is found that the limits of the blood urea nitrogen are only slightly higher in the arteriosclerotic group. Furthermore, there does not appear to be any appreciable difference in terminal kidney function between the cases of fairly marked arteriosclerosis and those of moderate degree. This might appear to be unusual, yet it is recognized that in kidneys with moderate diffuse or focal scarring there is compensatory hypertrophy of secretory tissue and consequently the functional capacity may be relatively unchanged; and, as MacCallum [14] has suggested, "Perhaps the majority of the cases in which the pathologist at autopsy writes down 'slight chronic nephritis' are only instances of such obsolete scars in the kidney whose cause is now impossible to tell." Consequently in the present series of cases it is apparent that the functional impairment present in the moderately arteriosclerotic group and also in the normal group, is, in all probability, largely due

to toxic influences associated with systemic disease rather than to demonstrable vascular changes. It has already been pointed out that most of the acute parenchymatous changes in the kidney do not appreciably affect either the injection method or the appearance of the arterial tree.

In the infarction group it is noteworthy that the blood showed some degree of urea nitrogen retention in every case. Although this suggests that infarction is responsible for lowering the functional efficiency, the series is too small to warrant such a conclusion.

In the syphilis group the percentage of normal blood urea nitrogen cases is somewhat lower than in Groups I and II, but, with the exception of one case associated with pyonephrosis, the blood urea nitrogen does not reach as high a figure as in either of the former groups.

A study of the urinalysis records on the entire series contributed nothing of further significance.

Summary

1. The injection of the renal vessels with a radiopaque suspension, and subsequent roentgenography of the kidney have proved a simple, easily accomplished procedure readily adaptable to the necropsy room as a means of reconstruction of the arterial tree including the glomeruli. This method does not interfere with the usual methods of gross and microscopic examination.

2. Roentgenographic results check accurately with the accepted anatomic conception of the arterial tree; and in the normal kidney the vessels show:

(*a*) A slender, gradually decreasing caliber of the lumen.

(*b*) Branching at an acute angle except at the primary division of the renal artery.

(*c*) Interlobar and arcuate arteries with gradual curves and arches like a spreading elm tree.

(*d*) Interlobular arteries which are slender, delicate, closely set and almost parallel, giving a thick uniform cortex.

(*e*) Glomeruli that are very fine and numerous, grouped evenly around the interlobular arteries, giving an appearance stereoscopically of slightly cone-shaped columns with the interlobular artery in the center and their bases toward the periphery of the cortex.

3. Severe arteriosclerosis is marked by:

(*a*) An uneven caliber of vessels with dilatations and constrictions.

(*b*) A branching angle which approaches a right angle.

(*c*) Interlobar and arcuate arteries which are wider, club-like and do not taper gradually. Their curves are abrupt and angular.

(*d*) Interlobular arteries which are fewer, shorter, tortuous, and do not run so perpendicularly to the cortex.

(*e*) Glomeruli that are larger, decreased in number, and clumped around areas of best vascular supply.

(*f*) With contraction of the kidney the cortex thins and the entire vascular tree appears drawn out from the hilum, and the picture of the arterial tree as a whole suggests a gnarled oak rather than a graceful elm.

(*g*) Milder degrees of sclerosis are found first in the periphery, *i. e.*, in the arcuate and interlobar arteries, and extend farther toward the hilum as the changes become more marked.

4. The vascular changes in syphilis, when present, were of the same appearance as those of arteriosclerosis in this series.

5. Examination by the injection method is of definite value in the study of thrombosis of vessels and infarcts.

6. A comparison of the roentgenographic appearance of the arterial tree with the urea nitrogen retention in the blood has failed to show a direct relationship between moderate arteriosclerosis *per se* and impaired renal function.

7. Acute nephritis, acute degenerative parenchymatous changes in the kidney tissue, and passive congestion have neither interfered with the injection procedure nor have they given a distinctive picture on the roentgenograms.

I wish to thank Dr. Eben C. Hill of the Department of Anatomy of Johns Hopkins Medical School for his kind assistance in the adaptation of his injection mass to this special work, without which the study would not have been possible.

I am also greatly indebted to Dr. J. R. Paul, Director of the Ayer Clinical Laboratory for his encouragement and constructive criticism throughout this work and to Drs. D. R. Bowen and P. A. Bishop of the Department of Roentgenology of the Pennsylvania Hospital for their kindness and coöperation in doing the roentgenography.

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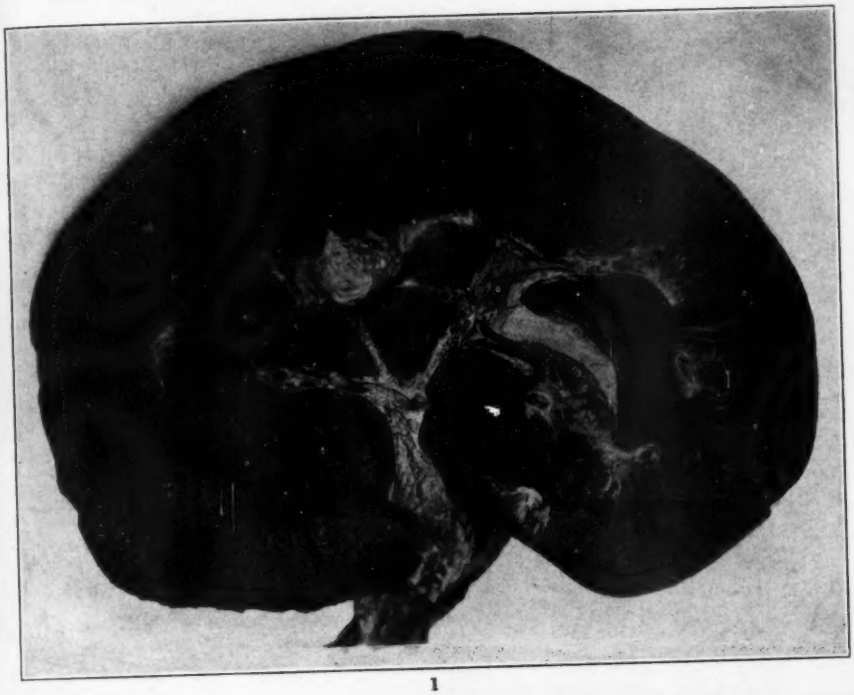
DESCRIPTION OF PLATES

PLATE 7

FIG. 1. Photograph of section of kidney showing appearance after injection. The specimen was cut, washed, and fixed in Klotz' solution so that the injected mass has been washed out of the larger vessels; but tiny vessels in the cortex and pyramids are well seen as fine lines, and the glomeruli appear as punctate points. See Fig. 6 for roentgenogram.

FIG. 2. Photomicrograph (very low power) of injected renal cortex showing the injection mass in interlobular arteries, in glomerular arteries and in glomeruli as dense black material. Note the anatomic arrangement of glomeruli around the interlobular artery.

FIG. 3. Photomicrograph (low power). Portion of an interlobular artery showing glomerular arteries arising from it and glomeruli filled with the injection mass.



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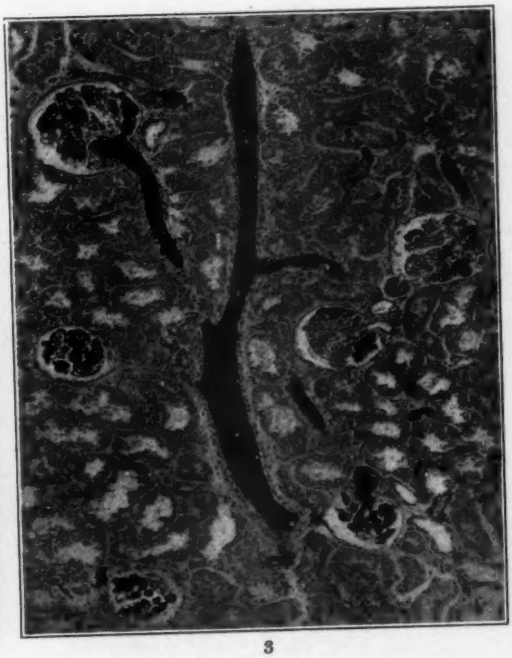

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Circulation in Normal and Pathologic Kidney

PLATE 8

FIG. 4. Photomicrograph (low power). A tangential section of the cortex showing the injection mass in interlobular arteries and glomeruli. Note the grouping of glomeruli around the interlobular vessels. The histologic study is not interfered with by the injected material.

FIG. 5. Roentgenogram of a normal arterial tree. Kidney from a boy, 14 years of age, dying of cardiac decompensation in active rheumatic fever.

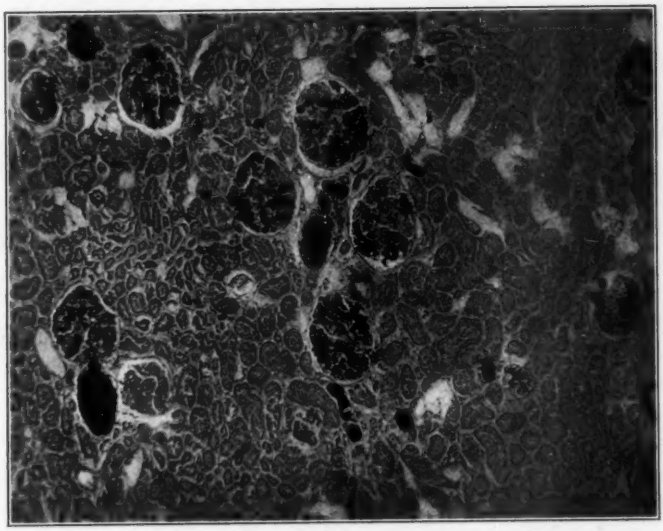

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PLATE 9

FIG. 6. Roentgenogram of a normal arterial tree. Kidney from a man, 40 years of age, dying of carcinoma of the liver. The apparent constriction of the origin of one of the large primary divisions of the renal artery is found stereoscopically to be due to an optical phenomenon on the flat view.

FIG. 7. Roentgenogram of a normal arterial tree with infarcts. One infarct is seen at the periphery of the cortex near the hilum as an irregular defect and another as a dark area in the middle of the opposite pole. The hollows of the pyramids are well seen. Kidney from an 8-year-old girl dying twenty-eight days following extensive third degree burns of the body and extremities.

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Graham Circulation in Normal and Pathologic Kidney

PLATE 10

FIG. 8. Roentgenogram of a normal arterial tree with infarcts. Three rather large defects in the cortical injection are seen at the periphery of the upper pole, and two deep in the region of the lower calyx near the hilum. These were white infarcts grossly. Kidney from a patient 27 years of age dying of vegetative endocarditis.

FIG. 9. Roentgenogram of a kidney with subacute nephritis, "large white kidney." The arterial tree is normal and the injection complete and heavy.

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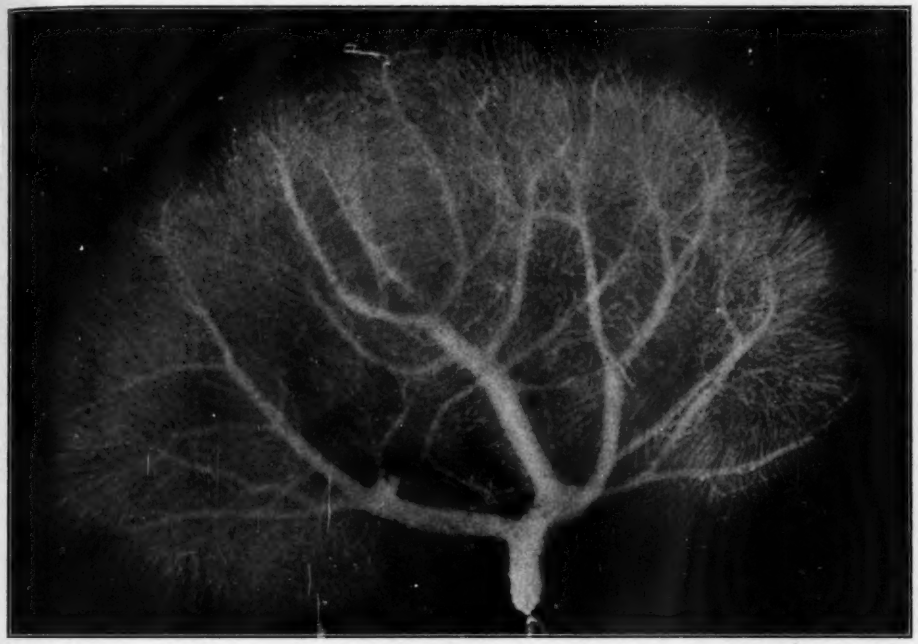
Graham Circulation in Normal and Pathologic Kidney

PLATE 11

FIG. 10. Roentgenogram of a kidney showing apparently complete injection of the pyramidal vessels. The arterial tree is normal. Kidney from a woman, 33 years of age, dying of gangrenous endometritis. Histologically there was marked passive congestion and cloudy swelling.

FIG. 11. Roentgenogram of a severely contracted kidney (nephrosclerosis). Note the uneven lumina and "dead tree" appearance of the vessels and the relatively few and very large glomeruli. A large retention cyst is seen on the periphery opposite the lower border of the hilum. Kidney from a man, 55 years of age, having generalized arteriosclerosis and dying of uremia.



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Graham Circulation in Normal and Pathologic Kidney

Plate 12

Fig. 12. Roentgenogram of a kidney, the vessels of which show moderate arteriosclerosis. Changes are most marked peripherally, the cortex is narrow, and the arcuate and interlobar vessels are tortuous with widened lumina, and end abruptly. Kidney from a woman, 70 years of age, with generalized arteriosclerosis, dying of cerebral thrombosis with infarction.

Fig. 13. Roentgenogram (small area enlarged $2\frac{1}{4}$ times) of normal arterial tree to show the details of the delicate tapering structure of the interlobar and arcuate arteries, and the small, very straight interlobular arteries almost hidden by surrounding clumps of glomeruli.

Fig. 14. Small area of roentgenogram of Fig. 9 (enlarged $2\frac{1}{4}$ times). The thick cortex shows the column-like appearance produced by glomeruli clumped around the interlobular arteries.

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Plate 13

Fig. 15. Small area of roentgenogram of Fig. 10 (enlarged $2\frac{1}{4}$ times). The vessels of the pyramids, broad and feathery at the base and narrowing as they converge toward the tip, are well shown.

Fig. 16. Small area of roentgenogram of Fig. 11 (enlarged $2\frac{1}{4}$ times). Note the few and very large glomeruli in the narrowed cortex.

Fig. 17. Small area of roentgenogram of Fig. 12 (enlarged $2\frac{1}{4}$ times). The tortuosity and uneven dilatation of the lumina of interlobar and arcuate arteries is clearly seen. The glomeruli do not appear increased in size.

Fig. 18. Roentgenogram (small area enlarged $2\frac{1}{4}$ times) of a contracted kidney of chronic nephritis. Note the relatively mild sclerotic changes in the arterial tree, the rather wide cortex containing but few greatly enlarged glomeruli and the fairly complete injection of the pyramidal vessels. Compare the appearance here with that of a contracted nephrosclerotic kidney in Fig. 16.

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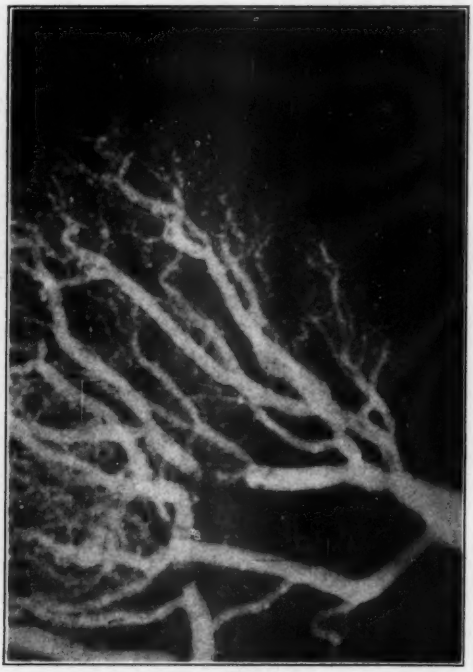

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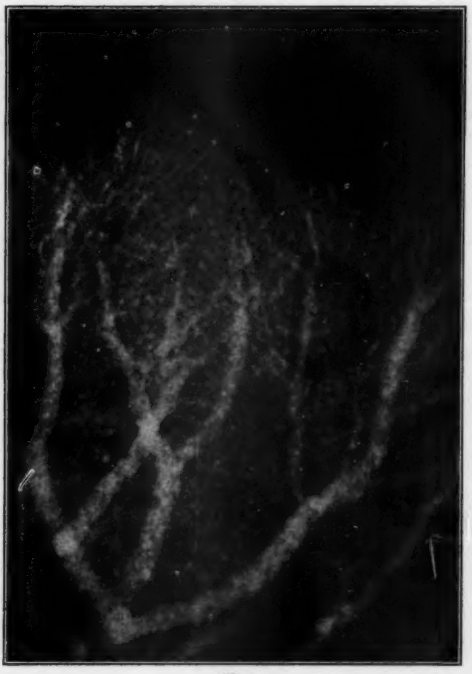

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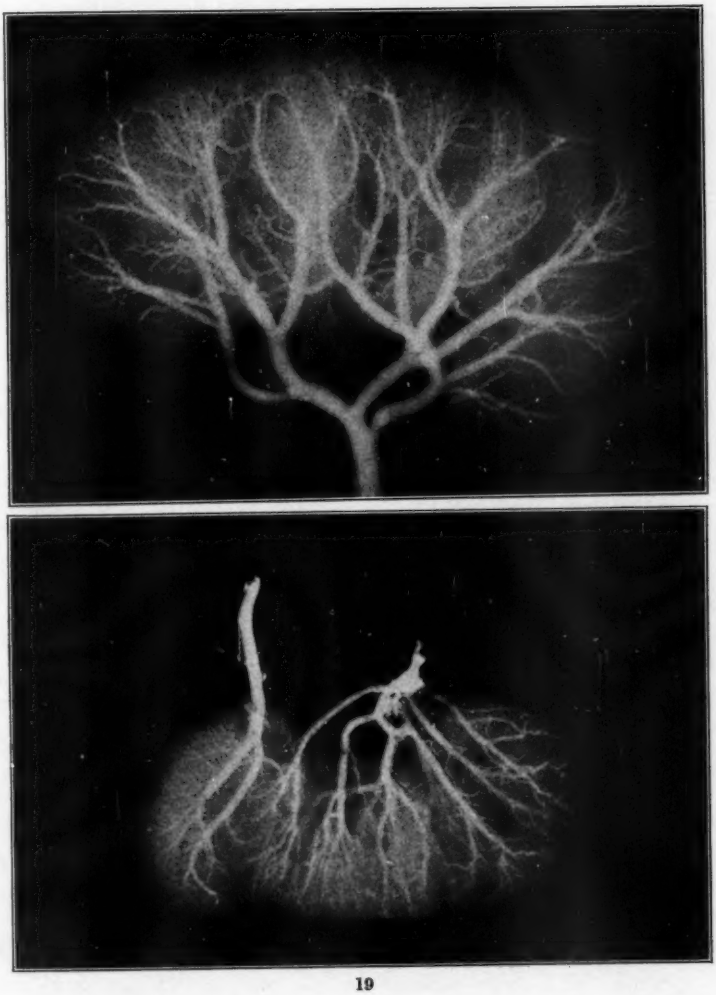
Graham

Circulation in Normal and Pathologic Kidney

Plate 14

Fig. 19. Roentgenograms of both kidneys from a case of aneurysm of the aorta at the level of the renal arteries. The left renal artery was thrombosed and injection distal to the thrombus in the upper two thirds, shows a shrunken kidney and a shriveled arterial tree with no glomeruli injected. The lower pole supplied by an anomalous artery is larger and normal in appearance and the line of division is sharply drawn. The renal pelvis is faintly visualized by some of the injection mass which appeared in the pelvis during the arterial injection.

The right kidney is hypertrophied. Well defined hollows are seen where pyramids (uninjected) occur. There are mild sclerotic changes in the arcuate and interlobar arteries. The patient was 45 years of age.



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THE ETIOLOGY AND PATHOLOGY OF PYELITIS CYSTICA, URETERITIS CYSTICA AND CYSTITIS CYSTICA *

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Cysts of the mucous membrane of the renal pelvis, ureters and urinary bladder have long been recognized. They rarely produce clinically recognizable phenomena but among pathologists and surgeons their etiology, occurrence and evolution have been much in dispute. This study was undertaken to review and correlate these different opinions.

REVIEW OF THE LITERATURE

In the pathologic work of Morgagni [28] in 1761 is found the first reference to this condition. He reported two cases, one in a man aged 60 and the other in "a decrepit old man who for many years had been afflicted with lues venerea." In both cases there was bilateral hydronephrosis and hydro-ureter. He described his observations in the first case: "on feeling the ureters, the sensation of there being calculi in some parts of them was communicated, but when they were slit open, an hydatid was found in every one of the places. Some were round, others were oval, hanging from the inner coat into the canal of the ureter, but not by a small stalk. The round ones were equal in size to very small grapes and the oval hydatids were double the length of the others."

The next case to be found in the literature was reported by Johnson [20] in 1816. His case was that of a woman; hydronephrosis and hydro-ureter were present on the same side as the cysts.

Rayer,[34] in 1837, and Rokitansky,[35] in 1861, reported cases of this condition. Rokitansky says: "Cysts appear to be more frequent in the urinary passages than they are in and upon other excretory ducts. Without referring to the other cases, we may notice two that have

* Thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Urology, June, 1925.

Received for publication September 22, 1927.

been observed in the Vienna Hospital. They represent cysts, the size of millet seeds or peas, developed under the mucous membrane and either grouped together or solitary, containing a colorless or yellowish serous fluid in which is found a soft glutinous or hard nodule varying in size and resembling amber. These cysts and their mucous covering occasionally burst, which is proved by the concretions having been discovered unattached in the bladder. They were chiefly found occupying the ureters and in one case the pelvis and calices of the kidney." Neither Rayer nor Rokitansky expresses definite views as to the origin of the cysts.

Virchow,[43] in 1863, described a case and compared the cysts to the mucous cysts of the vagina.

Egli,[11] in 1873, in a study of the histology of the renal pelvis, described flat globular glands resembling sebaceous glands, but these were inconstant in their occurrence.

In 1876 Litten [24] offered the first microscopic description of these cysts, but failed to see or make note of any cell nests. He was definite in his conclusions that these cysts were formed by an inflammatory blocking of the mucous glands and crypts of the mucous membrane, the retention of the secretion in these glands and crypts forming the cysts.

Hamburger,[15] in 1880, also described glands of the renal pelvis and ureters but stated that they were not a constant structure.

Ebstein,[10] in 1882, reported a case of cysts of the renal pelvis and ureter and supported Litten's views concerning their origin.

Limbeck,[23] in 1887, reported a case of cysts of the ureter. He was unable to find glands in the mucous membrane of the ureter and concluded that the cystic formations in his case were due to the agglutination of the proliferated mucous membrane and also to the central degeneration and liquefaction of sprouts of epithelium from the deeper layers of the mucous membrane. He did not deny that cysts are formed by the inflammatory blocking of mucous glands.

In 1889 Eve [12] published the first article in English literature on this condition. He reported a case and described ovoid bodies constantly found in the colloid contents of the cysts, which corresponded in size and appearance to pseudonavicellae. This observation convinced him of the parasitic origin of these cysts. He was supported in this view by Bland-Sutton,[5] Clark,[7] Voelcker,[42] Pisenti,[33] von Kahlden [21] and Morris.[29] In Osler's [31] textbook, as late as the ninth

edition in 1920, psorospermiasis of the kidneys and ureter is mentioned.

Silcock [38] was the only English writer up to 1889 who disagreed with the theory of parasitic origin. He described foci of epidermal cells in which a lumen was formed by degeneration of the central cells.

In the meantime, von Brunn [6] published his noteworthy article. He described epithelial bodies lying below the mucous membrane. Those showing an epithelial connection with the surface epithelium he designated epithelial buds or sprouts and those showing no connection he designated epithelial cell nests. He stated that these epithelial nests and buds were formed by the downward proliferation of the epithelium in the form of sprouts, and their subsequent separation from the mucosal lining. He believed that this proliferation of the epithelium was stimulated by inflammation. In proof of these statements, he said he was unable to find glandular elements, that the epithelium forming the nests was similar in every respect to the surface epithelium, and there was no constant lumen or exit duct, nor were the changes ordinarily seen in secretory epithelium present in the cells. The cystic formation he believed to be due to the degeneration of the central cells of the nests.

Lubarsch [26] shortly afterward confirmed the observations of von Brunn and reported two cases of ureteritis cystica and ten cases of cystitis cystica. He said that the microscopic appearance and the staining reaction of the contents proved that cysts were formed by degeneration of the central cells. In his cases, he found cysts originating in three separate ways: (1) from von Brunn's cell nests; (2) from the inflammatory closure of the crypts of the mucous membrane, and (3) apparently from abnormally placed glands of the upper urethra.

Aschoff [3] reported a case of ureteritis cystica and agreed with Lubarsch in his views regarding the formation of cysts from von Brunn's cell nests. He examined the ureters and bladder in a boy aged 1½ years, and a girl aged 3 years, but was unable to find either epithelial buds or cell nests or cysts. On further study, he was unable to find glandular formations above the internal sphincter of the urethra. He concluded that von Brunn's cell nests were of inflammatory origin and showed a predilection for the calices of the renal pelvis, the ureteropelvic juncture and the neck of the bladder. He

believed that these nests of von Brunn were formed in two ways: by proliferation downward of the deeper layers of the epithelium of the urinary tract, and by proliferation of the fibrous connective tissue which grew upward and cut off islands or nests of the epithelium.

Marckwald [27] found ureteritis and cystitis cystica in a new-born child and maintained that an inflammatory process was not necessary to the formation of von Brunn's epithelial buds or cell nests.

Stoerk,[39] after a thorough study of thirteen cases of ureteritis and cystitis cystica, differed with Marckwald in that he considered the origin of von Brunn's cell nests to be inflammatory. He also disagreed with von Brunn, Lubarsch and Aschoff and considered the cystic formation to be a secretory phenomenon.

Following this, Radtke,[33] Motz and Cariani,[30] Liebreich,[22] and Harris [16] reported cases and supported von Brunn, Aschoff and Lubarsch in their conclusions.

Herxheimer [17] reported two cases of ureteritis and one case of cystitis cystica. He examined twenty-nine cases without gross cysts, making serial sections from selected situations in three. Von Brunn's cell nests or buds were found in eleven of the twenty-nine cases. Glandular elements were not found. Nests were not present when the subject was less than 2 years of age. In one case, a child aged 8 years, von Brunn's cell nests were found. No parasites were found in the cystic contents and the reaction for mucus was negative. He concluded that von Brunn's cell nests are the origin of the cysts, that they are not normal but are commonly present at any age, that they vary in number, size and distribution, and that they are the result of the proliferation of the mucous membrane of the urinary tract following an inflammatory process. The elimination of toxic substances is enough to cause this proliferation and explains the cell nests and cysts found by Marckwald in the new-born.

Giani [13] introduced into the bladder of rabbits by a suprapubic incision gelatin capsules containing bacilli of tuberculosis, for the study of tuberculosis of the urinary tract. In some instances the capsule passed from the urethra while in others it formed the nucleus for salty incrustation. On killing these rabbits he discovered a condition similar to cystitis cystica. Following this, he denuded areas of the bladder in twenty rabbits, using a Volkmann curet through a suprapubic wound. He killed the rabbits at different times from

forty-eight hours to two hundred seventy days afterward. Sections taken in forty-eight hours showed only scattered bits of epithelium remaining in the places curetted; in five days, granulation tissue and beginning proliferation of the remaining epithelium were evident; in ten days, the epithelium was spread out, practically covering the whole area; in fifteen days numerous mitotic figures were seen in the epithelial cells; in twenty-five days, epithelial buds or sprouts were present; in forty-five days, epithelial cell nests as well as the epithelial buds were present; in seventy-five days, the center of the epithelial cell nests stained poorly and in places a lumen was seen; in one hundred days, the cysts were increased in size and some were approaching the surface, and, with a magnifying glass, the cysts were just visible on the surface; in one hundred twenty days, the cysts were diminished in number; in one hundred sixty days, the mucosa was practically normal; in two hundred seventy days, all signs of the condition had disappeared. He concluded that any irritation of the mucous membrane will cause proliferation of the epithelium and the formation of von Brunn's epithelial buds and cell nests, and that after the nests have formed they progress to the point of forming cysts and eventually rupture into the lumen of the urinary tract even in the absence of the original irritation.

Since Giani's experiments, many papers have been written on pyelitis cystica, ureteritis cystica and cystitis cystica, and several cases reported. Notable among these were the papers of Stow,[41] Saltykow,[36] Albersloetter,[2] Augier and Lepoutre,[4] Hibbs, [18] and Jacobson.[19]

More than sixty cases of pyelitis cystica, ureteritis cystica, or cystitis cystica have been reported in the literature; cystitis cystica predominates. In many of these there were only a few cysts in the trigone of the bladder. Table I includes the most pronounced cases reported. The theories as to the cause of these conditions may be summarized as follows: (1) inflammatory closure of glands in the urinary tract; (2) inflammatory closure of crypts of the mucous membrane; (3) parasitic invasion of the urinary tract, and (4) degeneration of central epithelial cells or the secretory action of the epithelial cells of the epithelial cell nests of von Brunn.

There are likewise conflicting theories as to the formation of the epithelial cell nests of von Brunn which may be summarized thus: (1) That they are inflammatory in nature and are formed by down-

TABLE I

Marked Pyelitis, Ureteritis or Cystitis Cystica

Case	Author	Sex	Age, years	Urinary history	Urinary findings
1	Morgagni	M	60	Burning	Slight bilateral hydronephrosis and hydro-ureter. Cysts of renal pelvis and ureter (bilateral).
2	Morgagni	M	old man	Difficulty 12 years	Bilateral hydronephrosis and hydro-ureter. Right ureteral calculus; cysts of right ureter.
3	Litten	F	75		Right hydronephrosis and hydro-ureter. Right ureteral calculus; cysts of right ureter.
4	Lubarsch	M	75		Purulent pyelitis and cystitis. Dilated ureters. Vesical calculi. Cysts both ureters.
5	Lubarsch	F	78		Bilateral pyelonephritis. Ureters dilated and covered with cysts.
6	Ajutolo	F	40		Duplication of left kidney, pelvis and ureter. Lower pelvis and ureter dilated and showing cysts.
7	Ebstein	M	48	Suppuration of urinary passages; hematuria	Chronic pyelonephritis, ureteritis and cystitis. Left ureteral calculus. Cysts left renal pelvis and ureter.
8	Kahlden	F	66		Chronic interstitial nephritis with recent parenchymatous nephritis and cystitis. Cysts of upper right ureter.
9	Kahlden	M	67		Carcinoma of bladder. Cysts both ureters and renal pelvis.
10	Albersloetter	F	60		Bilateral hydronephrosis. Diverticulum of bladder with cystitis. Cysts both ureters.
11	Albersloetter	F	71		Vesical mucosa swollen and red; small blisters around neck. Cysts both ureters, especially right.
12	Liebreich	M	53	Hematuria	Ureters slightly dilated. Bladder dilated and hypertrophied. Cysts both ureters.
13	Herxheimer	M	25		Trabeculated and hypertrophied bladder. Bilateral slight hydronephrosis. Cysts both ureters.
14	Herxheimer	F	69		Pyelitis and ureteritis with necrosis of the renal papillae. Cysts of renal pelves and ureters.
15	Augier and Lepoutre	F	86		Pyelonephritis and ureteritis. Atrophic kidneys. Left hydronephrosis and hydro-ureter; cysts left ureter.

Case	Author	Sex	Age, years	Urinary history	Urinary findings
16	Motz and Cariani	M	71		Cystitis. Cysts of trigone and fundus of bladder.
17	Motz and Cariani	M	63		Carcinoma of penis. Duplication of left ureter. Cysts of left ureters.
18	Stow	F	40		Chronic cystitis. Pyelonephritis. Complete duplication of pelvis and ureter on both sides. Numerous cysts of all four ureters.
19	Silcock	M	20		Left kidney removed. Right ureteral calculus. Cysts of bladder.
20	Voelcker	M	73		Chronic interstitial nephritis with formation of numerous cysts. Cysts left renal pelvis and ureter.
21	Hibbs	M	25		Calculus in bladder. Bilateral hydronephrosis and hydro-ureter. Cysts both pelves and ureters.
22	Harris	F	58		Death following operation for right renal calculus. Inflammation of right ureter and bladder with dilatation of ureter. Cysts right ureter.
23	Harris	M	54		Died following operation for right renal calculus. Duplication of left pelvis and ureter with calculus in upper pelvis. Cysts in ureter to upper pelvis.
24	Clark	F			Left hydronephrosis. Cysts of upper left ureter, pelvis and bladder.
25	Eve	F	51	Frequency, hematuria	Cysts both pelves and ureters.
26	Stoerk	F	57		Chronic cystitis. Cysts of both ureters.
27	Stoerk	F	60		Pyelitis, ureteritis, and hemorrhagic cystitis. Right renal stone. Cysts in ureter and trigone of bladder.
28	Jacobson	M	83	Operation; prostatic trouble 8 years before death	Duplication left pelvis and ureters to middle third. Atrophic kidneys with evidence of old pyelonephritis. Cysts both ureters and pelves on both sides.
29	Jacobson	M	74	Nocturia 15 years	Cysts of bladder.
30	Jacobson	M	66	Prostatectomy 2 years before death	Old pyelonephritis and cystitis. Cysts of ureters and pelves.

ward proliferation of the epithelium, or proliferation of the connective tissue upward between the epithelial nests to cut off islands of epithelial cells, and (2) that they are at times normally found in the urinary tract.

Cases Studied

One hundred twenty-five cases were observed practically consecutively at necropsy and three cases recognized macroscopically as pyelitis cystica, ureteritis cystica and cystitis cystica.

In 100 of the 125 cases, sections were taken from each renal pelvis and ureter, and from the fundus and trigone of the urinary bladder. In the remaining twenty-five cases, the renal pelvis and ureters were removed intact and mounted. Sections were taken at seven different levels, namely, renal pelvis, ureteropelvic juncture, upper, middle and lower thirds of the ureter, the fundus and trigone of the bladder.

The average age of the 125 subjects was about 44½ years, the oldest being 88 years and the youngest a fetus born in the fifth month of pregnancy.

Macroscopically, cysts were not found in the group of 125 cases. Microscopically, the so-called epithelial buds and cell nests of von Brunn or cysts were found in varying numbers and situations in 108 of the 125 cases (86.4 per cent). In Table II is a brief summary of seventeen cases in which epithelial buds, cell nests or cysts were not found.

Inflammation as judged by lymphocytic infiltration, proliferation of fibrous connective tissue, and formation of new capillaries was found in 63 (58.25 per cent) of the 108 cases showing epithelial buds, cell nests or cysts, and in four (23.6 per cent) of the cases in which no evidence of epithelial buds, cell nests or cysts were found.

In ten of the twenty-five cases in which sections were taken at seven different levels, epithelial buds, nests or cysts were found in the renal pelvis in ten cases, in the upper ureter in fifteen cases, in the lower ureter in seven cases and in the bladder in twelve cases. This confirms Aschoff's opinion that they are most common in the renal pelvis, upper portion of the ureter and bladder.

Serial sections were made at different levels in fifteen cases to establish, if possible, the presence of glands or uniform connections between the epithelial cell nests and the surface epithelium, or the presence of ducts connecting the cystic formation with the lumen of the renal pelvis, ureter or bladder. The epithelial sprouts or buds,

TABLE II

Seventeen Cases: No Epithelial Buds, Nests or Cysts

Case	Sex	Age	Inflammation	Cause of death
1	M	Full term	Absent	Still birth.
2	M	One-half hour	Absent	Prematurity (sixth month).
3	M	Eighth month	Absent	Still birth.
4	F	Six days	Absent	Prematurity (sixth month).
5	F	Three months	Absent	Cardiac anomaly.
6	F	*Years* 4	In bladder	Enucleation of right eye for neuroblastoma of the retina. Terminal bronchopneumonia.
7	F	5	Absent	Repair of right diaphragmatic hernia.
8	M	12	Absent	Glioma of the cerebellum with internal hydrocephalus.
9	F	13	Absent	Generalized peritonitis from a ruptured appendix.
10	M	18	Absent	Anterior poliomyelitis.
11	M	26	Wall infiltrated with myelocytes and other cells	Myelogenous leukemia.
12	M	38	Absent	Exploration of brain tumor. Cystic glioma of right cerebrum.
13	M	42	Slight throughout	Cholecystectomy for subacute cholecystitis with cholelithiasis. Edema of brain.
14	F	53	Absent	Cholecystectomy and appendectomy for chronic cholecystitis and appendicitis. Generalized peritonitis.
15	F	56	Subacute cystitis	Carcinoma of the ovaries with metastasis to the omentum, right ureter, and supraclavicular lymph nodes.
16	F	61	Absent	Carcinoma of the rectum with perforation and generalized peritonitis.
17	M	77	Chronic throughout	Carcinoma of the pancreas with metastasis to the liver and pleura.

as their name implies, are connected with the surface epithelium. A duct-like connection was not seen between the cystic structure and the lumen of the renal pelvis, ureter or bladder. In all cases, cysts can be seen opening on the surface. They have ruptured spontaneously or possibly in sectioning; but when the latter occurs one sees the cysts close to the surface and a good portion of the cystic envelope has disappeared.

Glands were not found in the urinary tract in the routine slides or in the serial sections, except in the trigone, where they were close to the internal sphincter of the urethra. These glands have been thoroughly studied and described by Albarran,[1] Lowsley [25] and others. As a rule, they are straight tubular structures lined by a double layer of cuboidal cells. Occasionally, one sees a nodule in the trigone of the bladder which somewhat resembles a cyst but which on section proves to be an encapsulated adenoma.

Egli, Litten, Hamburger and others undoubtedly saw formations which resembled glands, that is, cystic formations lined by several layers of cells, the inner layer being columnar and arranged axially.

Stoerk and Zuckerkandl [40] did not call these glands, but believed the lumen to be produced by the secretory action of the cells. Dogiel [9] states that the surface epithelium of the urinary tract is secretory and in this Stoerk and Zuckerkandl support him in part. They state that the surface epithelium is secretory in some instances when there is increased vascularity due to inflammation, but that, whatever the secretion is, it is not mucous in character and may be only a product of degenerated epithelium. In secretions of the urinary tract, taken by catheterization and cystoscopy, they were never able to demonstrate a mucous reaction, whereas in the cystic contents there was a mucin reaction on a few occasions.

Occasionally, in these cases, I have found the surface epithelium to resemble secretory epithelium, it being columnar in type and the nuclei situated basally. In numerous specimens of the fresh cystic material, specially fixed and stained with mucin stains, I was unable to demonstrate a mucin reaction in any instance.

That the crypts of the mucous membrane may occasionally become closed off by proliferation of the fibrous tissue is easily conceivable when one sees the close proximity between the walls at the mouths of the crypts and the marked proliferation of fibrous tissue that takes place in many cases.

Those advancing the theory that these cysts are caused by parasites did so merely on the histologic appearance of certain ovoid bodies found in the cystic contents, which they maintained resembled certain coccidia. They were unable to culture these parasitic forms and, in the examination of the fresh contents of the cysts, no motile forms were found. These forms were never seen in the surrounding epithelium nor was it possible to produce the disease in animals from the contents of the cyst. Gilchrist,[14] in an exhaustive study of the so-called psorospermatic diseases of the skin, has shown that degenerating epithelium gives rise to particles that simulate and have been called psorosperms. It has been established by Giani that cysts form from the epithelial cell nests of von Brunn. The method of formation of these nests is not clear. Von Brunn, Aschoff, Lubarsch, Stoerk and many others have considered them inflammatory in nature, while Giani has proved experimentally that they form as the result of inflammation. Marckwald has stated that they are occasionally normal constituents and reports a case in which they were present in a new-born child, although Herxheimer explains this by the excretion of toxic substances in the urine. Giani also states that, once the epithelial cell nests have formed, the cell nests will go on to cystic formation and eventually disappear even in the absence of the original causative factor and all signs of inflammation.

In sixty-three (58.25 per cent) of the 108 cases in which epithelial buds, cell nests or cysts were present, inflammation was manifested by lymphocytic infiltration or fibrous tissue proliferation, while in only four (23.5 per cent) of the seventeen cases remaining was there evidence of inflammation.

Fifteen of the 125 patients were under 20 years of age. In five of these fifteen cases epithelial buds, cell nests or cysts were found. Table III gives a brief summary of these cases.

It has been stated that these cysts, although inflammatory in nature, may be formed by two separate reactions of the tissue to inflammation, that is, by the proliferation of the epithelium and by the proliferation of the fibrous connective tissue. That they are formed in most cases by a combination of the two seems the most probable deduction, as they go hand in hand in inflammation of the urinary tract.

The variation in the size of the cysts is explainable on a purely

mechanical basis; that is, the size of the cyst varies with the amount and strength of the surrounding fibrous envelope, which depends, as in other conditions, on the severity and chronicity of the inflammation.

Jacobson proposed another factor in the formation of these nests: with old age and the consequent arteriosclerotic changes, the muscular walls are undernourished, and consequent muscular atrophy and atony produce excessive infolding of the mucosa, which is more

TABLE III

Five Cases Showing Epithelial Buds, Nests or Cysts (patients under twenty years of age)

Case	Sex	Age, years	Inflammation	Cause of death
1	M	5	Present	Chronic otitis media with purulent meningitis; internal hydrocephalus.
2	F	15	Present	Exophthalmic goiter. Pyelonephritis with multiple cortical abscesses.
3	M	16	Present	Cellulitis of face and neck from a furuncle. Hemorrhagic bronchopneumonia. Thrombosis left jugular vein. Multiple abscesses left kidney.
4	F	17	Present	Extensive superficial burns. Extreme emaciation. Calcium deposits both kidneys.
5	M	18	Absent	Sarcoma left leg with metastasis to lungs, liver, small intestine, and right kidney.

easily cut off into nests by proliferation of fibrous connective tissue. The formation of nests in the absence of arteriosclerotic changes he attributes to the inflammatory closure of crypts. This theory does not hold, since, in the absence of arteriosclerosis, definite epithelial budding and nest formation have been demonstrated.

In these cases the mucosa of the urinary tract reacted in four separate ways or in any combination of these four: (1) by desquamation of its epithelium, as seen in acute inflammatory processes; (2) by a papillary overgrowth or, as it is sometimes called, villous cystitis; (3) by proliferation of the lower layer of the epithelium with the formation of epithelial buds or sprouts; and (4) by cornification of the epithelium or, as it is commonly known, leukoplakia.

Illustrative Cases

Case 1. A woman, aged 46, complained of a mass in the left lower portion of the abdomen. Eight years before, a ventral hernia had been repaired, and one year following this an operation was performed for intestinal adhesions. During the last two years, she had had attacks of crampy abdominal pain, which occurred two to three times a week and were associated with severe constipation. There was no history of urinary symptoms.

There was an incarcerated left inguinal hernia and a small umbilical hernia. The urine contained ten pus cells to a high power field. At operation these hernias were repaired and at that time cholecystitis and cholelithiasis were found. Fourteen days later, cholecystectomy was performed. Three days afterward the patient died.

At necropsy a left-sided subdiaphragmatic abscess and myocarditis were found, as well as acute nephritis implanted on chronic nephritis. The left renal pelvis and ureter on both sides showed isolated, bleb-like cysts up to 4 mm. in diameter, which contained a slightly brownish, gelatinous or sago-like substance (Fig. 1). Cysts were not found in the bladder.

Case 2. A woman, aged 76, complained of dizziness associated with numbness of the right forearm and hand for the previous six months. The peripheral arteries showed marked sclerosis. The cardiac dulness was increased. The systolic blood pressure was 194 and the diastolic 86. There was definite weakness of the muscles of the right hand and forearm. The specific gravity of the urine was 1.014; it was alkaline and gave a definite reaction for albumin. Microscopically, there were from one to fifteen pus cells in each high power field. The patient died four days after admission.

At necropsy acute nephritis superimposed on chronic nephritis, myocarditis with coronary sclerosis, chronic vegetative aortic and mitral endocarditis, general arteriosclerosis, chronic catarrhal cholecystitis and cholelithiasis and left nephrolithiasis were found. The left renal pelvis and ureter showed several translucent cyst-like formations, some of which appeared pedunculated and contained a yellowish gelatinous material (Fig. 2).

Case 3. A man, aged 64, complained of a general breakdown one year previously. At the time of this breakdown he was considerably

improved by treatment in a hospital for a month. The breakdown was characterized by dyspnea and edema of the lower extremities, both of which returned after dismissal from the hospital. In the year there had been a gradual increase in the severity of these symptoms and mental failure had progressed.

The patient was emaciated and dyspneic and came in a wheelchair. The right side of his face was flaccid and the tongue protruded to the left. The peripheral arteries were markedly sclerosed. The systolic blood pressure was 170 and the diastolic 110. The apex beat was diffuse and considerably to the left; a blowing systolic murmur was heard best over the pulmonic area. There was marked edema of the lower extremities. The urine was acid and its specific gravity 1.007; there was marked reaction for albumin. There were numerous granular and hyaline casts and from thirty to fifty pus cells in each high power field. The blood urea was 456 mg. for each 100 cc. Death ensued eighteen days after admission.

Necropsy showed marked generalized arteriosclerosis, cardiac hypertrophy and dilatation, atrophy and scarring of the kidneys, and multiple cortical cysts following old healed pyelonephritis. Both the renal pelvis and ureter on each side showed isolated cyst-like structures. Chronic cystitis was present, and the trigone showed multiple cyst-like formations (Fig. 3).

Discussion of Cases

Microscopic sections in these cases showed numerous epithelial cell nests and cysts in all stages of development associated with a diffuse inflammatory process. The lumen was filled with a colloid-like material in which red blood corpuscles and degenerated epithelial cells were seen. The lining of these macroscopic cysts, as a rule, consisted of a single or double layer of flat epithelial cells, resembling somewhat endothelial cells, surrounded by a dense fibrous tissue envelope.

It is rather hard to understand why epithelial cell nests and microscopic cysts are common while macroscopic cysts are so seldom found at necropsy. In a cystoscopic experience of any extent, it is rather common to find cysts of the mucosa of the bladder in cases of long-standing inflammatory disease. In the examination of the records of 190 cases of bilateral pyelonephritis, cystitis cystica was found in

thirty-three (17.4 per cent). The cysts are usually found in the trigone and base of the bladder but are occasionally diffusely scattered over the remainder of the mucosa.

This seemingly conflicting evidence is probably in part due to the fact that, unless carefully searched for, the smaller cysts are easily overlooked, particularly in the presence of marked inflammatory reaction.

Conclusions

1. Glandular structures are not normally found in the urinary tract above the trigone of the bladder.

2. Epithelial buds, cell nests, and cysts are not normally found in the urinary tract.

3. Cysts of the urinary tract are formed from the epithelial nests of von Brunn.

4. The epithelial buds and cell nests of von Brunn are inflammatory in nature.

5. Microscopically, epithelial buds, cell nests and cysts are present in the majority of persons more than 20 years of age.

6. This study does not reveal evidence to support the secretory theory of the formation of these cysts.

7. The cysts are formed by degeneration of the central cells of the epithelial cell nests.

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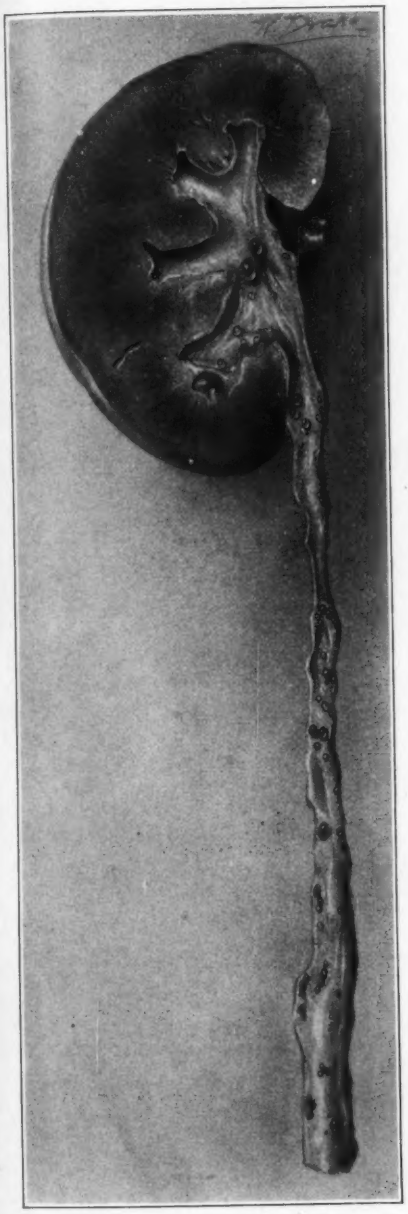
DESCRIPTION OF PLATE

PLATE 15

FIG. 1. Case 1. Left kidney and ureter. Cysts of the renal pelvis and ureter.

FIG. 2. Case 2. Left kidney and upper ureter. Calculus in upper calyx and cysts in the renal pelvis and ureter.



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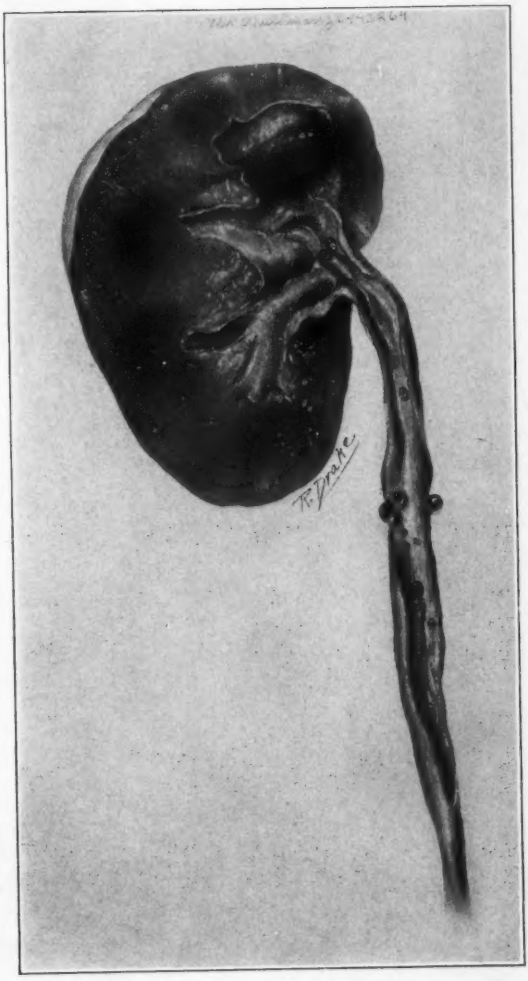

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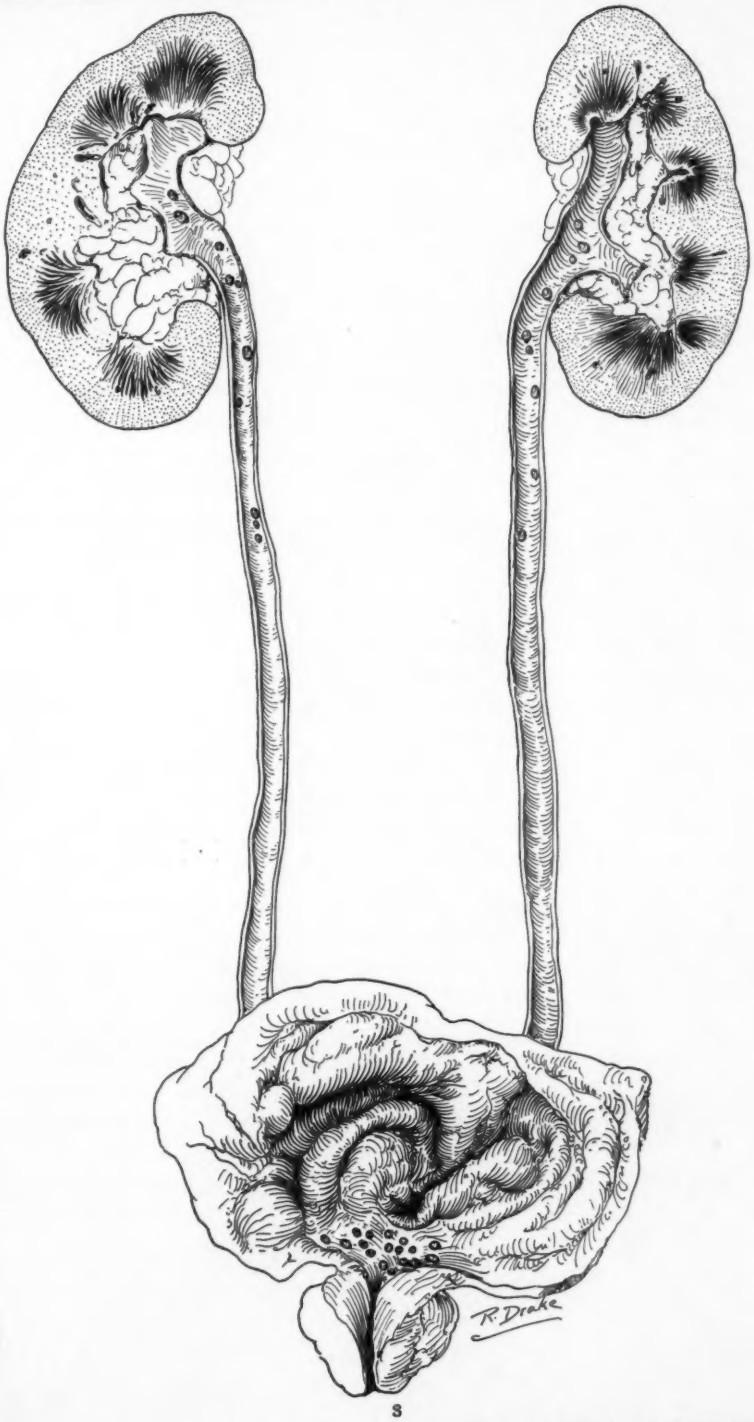
Morse

Pyelitis, Ureteritis and Cystitis Cystica

Plate 16

Fig. 3. Case 3. Kidneys, ureter and bladder; cysts of the renal pelvis, ureters and trigone of the bladder.



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Pyelitis, Ureteritis and Cystitis Cystica

A MALIGNANT TUMOR SIMULATING BONE MARROW*

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Heterotopia of the bone marrow is not an extremely rare lesion and usually is represented by small masses of myeloid tissue. Saleeby [1] has recently recorded a case found at necropsy and has briefly summarized the literature. Development of bone marrow in metaplastic bone is not an unusual finding. Thus it is encountered in old inflammatory processes, such as in the wall of an appendix, the site of a previous appendicitis, or in the walls of sclerotic arteries, in slowly-growing tumors and numerous other places.

Freudenstein [2] presents a careful study of the problem of the development of bone marrow in heterotopic bone and considers three theories as to its origin:

(1) Adventitious cells can produce the various cell forms of the marrow, even including the red blood cells.
(2) The elements of the normal bone marrow can circulate in the blood and be deposited in the regions of bone formation.
(3) In engorged capillaries or veins lymphocytes enlarge and become changed to typical large proliferating lymphocytes. From these develop intra- and extravascular myelocytes, red blood cells and megakaryocytes.

Heterotopic bone marrow has been not infrequently reported in the pelvis of the kidney or in the adrenals. These cases have usually been associated with myelogenous leukemia or the so-called splenic anemia.[3, 4, 5] Mieremet [6] reports a striking tumor, found in the adrenal of a man dying of carcinoma of the esophagus, showing the histologic structure of fat cells separating myelocytes, myeloblasts, erythrocytes, erythroblasts, polymorphonuclear leucocytes and megakaryocytes. Heterotopic marrow may occur also in connection with endotheliomas. Thus in an actively growing endothelial tumor of the liver, Fischer [7] found islands of blood-forming tissue containing nucleated blood cells and myelocytes.

* Received for publication August 26, 1927.

In none of these cases, however, have the masses of heterotopic marrow presented other than a chance association with the cause of death. The following case presents such unique features that it seems worth while to place it on record.

Report of Case *

Clinical History: J. J., 42 years of age. In November 1925 patient, an unmarried white female, was run down and in a poor condition. On examination sugar was found in her urine. With 45 units of insulin daily, she became and remained sugar free although the blood sugar was not reduced below 250 mg. Her spleen was enlarged and the red cell count varied in the neighborhood of 2,000,000, with many immature forms, whereas her white cell count ranged about 8,000. While getting out of bed she struck her nose, causing uncontrollable hemorrhage which resulted in her death.

Necropsy Report

H–26–166. *Body:* The body is that of a well developed and extremely obese white woman. External examination is negative except for bloody fluid in her nose and a small firm mass adherent to the outer border of the left sixth rib near the costochondral junction.

Peritoneal Cavity: The peritoneal cavity contains a small amount of thin blood-tinged fluid. The mesenteric lymph nodes are not enlarged.

Pleural Cavities: There is about one liter of thin blood-tinged fluid in each pleural cavity. On the inner surface of the chest wall are several smooth, rounded swellings firmly adherent to the periosteum of the ribs. These measure about 3 × 1.5 × 1.5 cm. On section they are pale pink, friable, soft and of uniform appearance and connected with the substernal mass about to be described. The under surface of the sternum, particularly at its upper end, and the adjacent portions of the costal cartilages are covered over with a firm, very dark red, apparently hemorrhagic mass 1 to 2 mm. thick at the edges and gradually thickening toward the center where it reaches a depth of 1 cm.

Heart and Pericardial Cavity: Negative.

Lungs: Essentially negative.

Spleen: Weight 1500 gm. There are a number of fibrous adhesions to the parietal peritoneum. On section the organ is very soft

* This case was summarized in the Cabot case records, Boston M. & S. J., 1927, cxcvi, 657.

and purplish red in color. All the normal markings are obscured and the pulp drips from the cut surface.

Liver: Weight 5400 gm. Capsule is smooth and the liver is pale, of an opaque yellowish gray color. On section it cuts readily and the markings are fairly distinct with slight exaggeration of the usual lobular appearance. The cut surface and the knife are greasy.

Gall Bladder: The gall bladder contains two rounded soft, yellow-brown stones 0.5 cm. in diameter.

Gastro Intestinal Tract: Negative.

Pancreas: Negative.

Kidneys: The left kidney weighs 175 gm. It is adherent to its bed but the capsule strips fairly easily, leaving a smooth surface. The ureter is seen to be greatly thickened and a red fleshy substance is present in the hilum of the kidney. When sectioned a red fleshy mass is revealed between the pelvis and the kidney tissue, ranging from 0.3 to 1.5 cm. in thickness. At no point has it ulcerated through into the pelvis and it is apparently not invading the kidney tissue, but rather insinuating itself between the parenchyma and the epithelium of the pelvis. This mass is extending beneath the pelvic epithelium and its edge is distinctly hemorrhagic. The cortex is 1.8 cm. thick. The glomeruli are visible as minute specks. The pyramids are not particularly well marked. The same description is true for the right kidney with the exception that it weighs 225 gm., and that the tumor mass is slightly more extensive. Both ureters are encased in a firm reddish mass continuous with that described beneath the pelvic epithelium, and extending the entire length of the ureters into the reddish mass which becomes merged with the pelvic musculature. There is no obstruction to the lumen of either ureter and so far as can be determined no ulceration into their lumina.

Adrenals: Negative.

Bladder: Negative.

Genitalia: Essentially negative.

Pelvis: The entire pelvic musculature including the psoas, iliacus and the levator ani is merged into the firm reddish mass continuous with the growth described about the ureters. It is entirely retroperitoneal. On section the tissue is dark red but contains rather sharply defined pale foci varying in size and shape. The consistence is apparently the same throughout. There is no continuity with or invasion of the rectum or the other pelvic organs.

Lymph Nodes: The retroperitoneal lymph nodes from the pelvic floor to the diaphragm are enlarged. Some are soft, pale pink and friable while others are very firm and dark red. There is practically a continuous cord of tumor tissue connecting the retroperitoneal lymph nodes and extending into the mediastinum. The mediastinal lymph nodes present a similarly varied appearance and are involved in the same process as those below the diaphragm. There is one very firm lymph node about 1 cm. in diameter beside the head of the pancreas. On section this node shows marked carbon pigmentation.

Aorta: There are a few atheromatous plaques in the abdominal portion of the aorta, one of which has become calcified.

Bone Marrow: The bone marrow of the ribs is a pale pink, that of the bodies of the vertebrae is somewhat darker, but shows no apparent variation from the normal.

Microscopic Examination

Heart: Essentially negative.

Lungs: Pleura slightly thickened and, in one small focus, contains clusters of cells, some of which resemble lymphocytes and plasma cells, others endothelial leucocytes, and others eosinophiles and eosinophilic myelocytes. Lung capillaries are congested and a few megakaryocytes are present in them.

Spleen: But few lymph nodules can be distinguished. Marked congestion. Numerous clusters of large cells with vesicular nuclei and relatively small amounts of pale cytoplasm are scattered through the pulp together with nucleated red cells in various stages of development, eosinophiles and eosinophilic myelocytes (Fig. 1).

Pancreas: Lobules are separated by fat tissue. Slight increase in interacinar connective tissue. Islands are few but most appear normal though some contain considerable amounts of hyaline material. The peripancreatic fat is infiltrated by cells with large clear nuclei similar to those described above, by nucleated red cells and by neutrophilic and eosinophilic myelocytes.

Liver: Many of the liver cells contain large vacuoles. The nuclei of a considerable number are swollen and clear with relatively small masses of chromatin. The portal regions are infiltrated by cells with but little cytoplasm whose large nuclei contain scattered chromatin granules, by nucleated and a few non-nucleated red cells and by eosinophilic myelocytes. An occasional megakaryocyte is present.

Small islands of similar cells occur in many of the sinusoids. The nuclei of the endothelial cells lining the sinusoids are rounded and prominent. The histologic picture is strikingly like that seen in the liver of myelogenous leukemia.

Kidney: Slight postmortem change. Glomeruli negative. Colloid degeneration of tubular epithelium. There is some vacuolization of the epithelium of Henle's loops due to glycogenic infiltration resulting from diabetes. The region of the pelvis contains a large mass of hematopoietic tissue which under low power resembles hyperplastic marrow, showing scattered fat cells throughout. One small spicule of bone is present in the pelvic region. Under high power sinusoids can be made out. There are numerous red blood cells in all stages of development. Eosinophilic myelocytes and megakaryocytes (Fig. 2) are also present. The most common nucleated cell is similar to that already described in pleura, spleen and liver. This cell appears to be the hemocytoblast. The hematopoietic tissue is seen to penetrate the kidney substance for some distance, usually in close relation to the larger blood vessels.

Adrenal: There is a considerable amount of hematopoietic tissue in the surrounding fat.

Ureter: The wall of the ureter is infiltrated and greatly thickened by hematopoietic tissue similar to that described in the kidney (Fig. 3). The mucosa and muscularis mucosae are not involved.

Pelvic Musculature: Here and there strands of fibrous tissue and of muscle fibers, some of which are necrotic, traverse a mass of hematopoietic tissue. In one section a portion of the lumbar plexus is present and the perineurium is penetrated by the bloodforming tissue in several places.

Uterus: Cells with large vesicular nuclei similar to those described in the liver, spleen and kidney, surround the arteries and penetrate the musculature to some extent. The mucosa is atrophic.

Lymph Nodes: The sinuses are infiltrated by rather large cells similar to those described elsewhere.

Substernal Mass: This same type of large cell together with great numbers of red blood cells infiltrate the connective tissue. The appearance is almost hemorrhagic in places. In other regions among the more primitive cells are scattered eosinophilic and neutrophilic myelocytes, nucleated red cells, and megakaryocytes. The capillaries are large and somewhat tortuous.

Bone Marrow: The marrow is not remarkable and very few of the primitive type of cell, so common in the abnormal marrow-like tissue, are found. Unfortunately, fixation is extremely poor.

Discussion

The exact nature of this tumor is uncertain. It obviously is a tumor and not a concomitant phenomenon of a leukemia or other disease involving the hematopoietic system. The histologic structure and the clinical history would lead to the belief that these cells did not gain access to the circulation in any considerable amount and that the anemia present was secondary anemia such as might be associated with any advanced malignant tumor. The widespread distribution of the lesions suggests a very malignant type. It is striking that all parts of the tumor, even the mass beneath the sternum, are continuous with one another.

Just what proportion of the symptoms noted in her illness of four months is referable to her co-existent diabetes is uncertain. However, the fact that she did not show much clinical improvement with insulin treatment leads to the belief that most of her symptoms were due to the growth of the tumor. The large proportion of the reported cases of heterotopic marrow which are found in the kidney pelvis suggests that here may be the primary site of this tumor.

Curiously enough, Jordan and Speidel [8] bring out phylogenetic evidence as to the myeloid function of the kidney. They state that in the tadpole the kidney is the chief lymphomyeloid organ. The hematopoietic activity is centered in the intertubular connective tissue (mesonephros). There are transition forms present between lymphocytes, red blood cells and granulocytes. In the adult frog the mesonephros produces chiefly granulocytes, and those in small numbers, while the spleen has become the important hematopoietic organ. Whether there is any relationship between this condition in the frog and the tendency of heterotopic marrow to occur in the kidney of man is of course purely speculative, but nevertheless worthy of passing mention. In the light of this it is quite possible that the tumor was primary in the pelves of the kidneys and extended down the ureters, spreading by way of the lymphatic system through the retroperitoneal and mediastinal tissues and ultimately reaching the spleen and liver. When heterotopic marrow occurs in a kidney it is usually found in both.

Another possible source, however, is the retroperitoneal fat tissue. Petri [9] in an examination of the retroperitoneal adipose tissue of forty adults, most of whom had died from infection or sepsis, but including also some cases of pernicious anemia, leukemia and tumors, found thirty-one to show small hemorrhagic lesions varying in size from a pinhead to a bean and having the appearance of hemorrhagic lymph nodes. Microscopically the islands were seen to be composed of relatively undifferentiated cells among which could be seen evidence of hematopoiesis of both the lymphocytic and the myelocytic series. He considers this adipose tissue as mesenchymal reticuloendothelial tissue which retains the embryonic potentialities of hematopoiesis. He believes the change to be induced in the adipose tissue by the action of toxic or bacterial stimuli. It is certainly true in this case that the retroperitoneal adipose tissue would more nearly represent the center of the neoplastic tissue than would the kidney pelves.

As to the nature of the tumor growth itself, it is very difficult to determine. Judging from the tendency to take on the typical morphology of bone marrow including fat cells and even (in the case of the hilum of the kidney) spicules of bone, it might be considered a myeloma of the mixed cell type. The predominant cell appears to be the hemocytoblast of Maximow although it is very difficult to identify positively. The bulk of the tumor is made up of relatively large cells with large nuclei, poor in chromatin, and a relatively small amount of cytoplasm free from granules which suggests the hemocytoblast or *Stammzell*. The other cells present, namely, erythroblasts, erythrocytes, megakaryocytes and cells of the polymorphonuclear series suggest also that a very primitive cell form makes up the bulk of the tumor and that this primitive cell is differentiating to the more specialized cell types in the growth process. There are certain cells in the tumor strongly suggesting lymphocytes. Unfortunately, the length of time postmortem (ten hours) has interfered with satisfactory oxidase reactions so that morphology alone can be relied upon. Should these cells be lymphocytes this tumor would provide evidence for the monophyletic origin of the blood cells. For lack of a better term the name hemocytoblastoma is suggested for this tumor.

SUMMARY

1. A case of an extensive tumor resembling bone marrow, apparently primary either in the pelves of the kidneys or the retroperitoneal fat tissue is reported in a woman 42 years of age without evidence of leukemic involvement.

2. The possible sources of origin and the nature of this tumor are considered.

3. The name hemocytoblastoma is proposed.

The writer wishes to acknowledge the interest of Dr. William B. Breed under whose care this patient was, and also his indebtedness to the House of the Good Samaritan where the necropsy was done.

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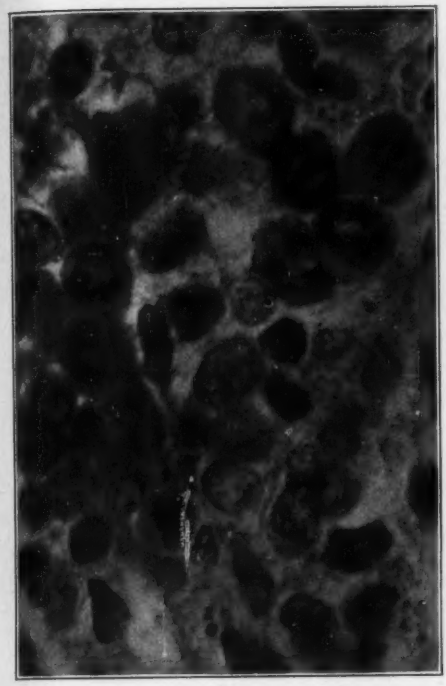
DESCRIPTION OF PLATE

PLATE 17

FIG. 1. Spleen. Note mitosis in erythroblast. × 1250.
FIG. 2. Kidney. Megakaryocyte. × 1250.
FIG. 3. Ureter. Drawing showing different types of cells. × 1500.



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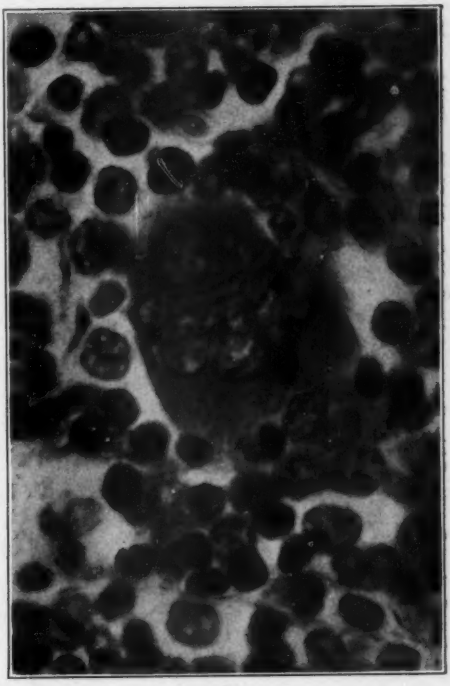

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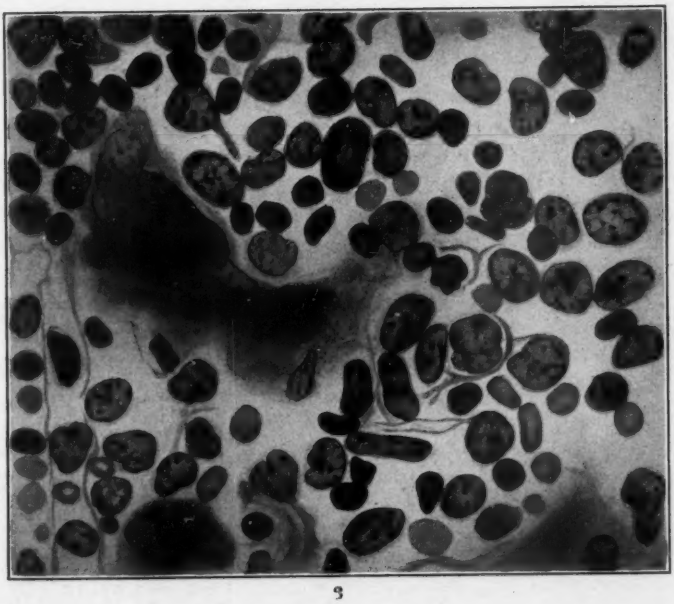

3

CONCERNING ECTOPIC CHORIONEPITHELIOMA *

REPORT OF TWO CASES

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Marchand [1] in 1895 in describing neoplasms hitherto known as "decidual" tumors, having clearly shown the relation of the tumor cells to chorionic elements, was the first to designate such structures by the term "chorionepitheliomas." The chorionic and the tumor cells are rather similar morphologically, and furthermore a relationship to pregnancy and especially to hydatidiform mole is recognizable. The tumors described by Marchand all developed in the uterus and gave rise to many and varied metastases, but in 1902, Zagorjanski-Kissel [2] gathered from the literature reports of nine cases; in eight the tumor appeared primarily in the vaginal wall, and in the other case neoplastic foci were found in the lungs and brain without a primary tumor of the genitalia. In Zagorjanski-Kissel's paper and in subsequent studies the view is more and more clearly expressed that there are instances where chorionepithelioma does not arise at the site of placental attachment but rather in distant foci, probably originating from chorionic cells or villi which have penetrated maternal vessels and have been more or less diffusely deposited. Dunger [3] spoke of such instances as examples of "ectopic chorionepitheliomas."

It is well known that chorionic elements may penetrate the maternal circulation. Schmorl [4] examined the lungs of 158 patients dying at different stages of pregnancy or after delivery, and found chorionic cells in the lung capillaries in eighty per cent of the normal pregnancies. In the lungs of eclamptics, chorionic cells obstructed capillaries, sometimes extensively, in every case examined. During the early period of pregnancy emboli of chorionic origin were found in the lungs in three out of twenty-five cases. Twenty-two cases dying after abortion during the first two months of pregnancy

* Received for publication September 14, 1927.

showed chorionic cells in the lung capillaries of eight, occurring twice in large numbers. In only three cases were evidences of chorionic cell proliferation in the lung observed, and in view of the lack of examination of the placenta, hydatidiform or chorionepitheliomatous changes could not be excluded. Apparently entire chorionic villi may enter the circulation and reach distant foci only in instances of protracted labor, manual removal of the placenta or ruptured uterus. Schmorl noted large numbers of chorionic cells in the lung capillaries and found evidences of proliferation in two cases of hydatidiform mole and in one of partial mole. In accordance with these findings he emphasizes the possibility that ectopic chorionepithelioma may originate from a previous mole or chorionepitheliomatous proliferation of a placenta completely expelled by labor.

Marchand [5] and Pick,[6,7] however, maintain that chorionic cells or villi deposited during normal pregnancy may likewise give rise to chorionepithelioma and that most cases of ectopic chorionepithelioma reveal a history of normal pregnancy, a mole being relatively rare. Attempts to produce chorionepithelioma experimentally in animals (Fraenkel [8]) have failed. This investigator injected ground placenta and mixtures of placenta and ovary subcutaneously, intraperitoneally and intravenously in rabbits and guinea pigs. Some animals were observed over a four-year period but no tumors occurred, the injected material undergoing necrosis or absorption. These experiments have little bearing, however, since certain factors other than the mere presence of chorionic elements in various organs are operative in the genesis of tumors, and, moreover, the animals used are not known to have spontaneous chorionepitheliomas. The opinions of Marchand and Pick receive support from an observation by Walthard.[9] The latter found a chorionepitheliomatous nodule in the vaginal wall of a patient during the eighth month of her fifth pregnancy. Caesarian section and total hysterectomy were performed and no evidences of either tumor or mole were found in the uterus. Death occurred seven months later with chorionepitheliomatous nodules in lungs, liver and left kidney. The author considers the nodules to be metastases from a primary ectopic chorionepithelioma of the vagina developing along with normal pregnancy. This interpretation is nevertheless questionable because there are observations on record of chorionepitheliomas, both uterine and ectopic, with very long latent periods. Koritschoner,[10] for ex-

ample, reported an ectopic chorionepithelioma twenty-two years after the last delivery, and Polano[11] reported one thirteen years after parturition. Ries[12] noted in a vein of the uterine wall a fairly well preserved chorionic villus eighteen years postpartum.

Chorionepithelioma may occur where there is no history of pregnancy. It may likewise develop in the testis and morphologically resemble the chorionepithelioma of the female. This tumor may also appear primarily in the ovary without previous pregnancy.

Cases of ovarian chorionepithelioma were first reported by Pick.[6,7] The first, an ovarian dermoid in a patient 30 years of age, showed in places typical chorionepitheliomatous proliferation; the second was an ovarian teratoma in a 9-year-old girl, and portions of this tumor structurally resembled chorionepithelioma. Since Pick's cases were reported, others have appeared in which the possibility of previous pregnancy can be absolutely excluded. Pick and likewise Schlagenhaufer[13] are of the opinion that embryonic elements are present in such teratomas which give rise to the chorionepitheliomatous proliferation, the tumor then developing like a uterine chorionepithelioma. Risel[14] and Mönckeberg[15] suggest that the proliferation begins in the ectodermal portion of the teratoma itself without the presence or development of embryonic cells. Such tumors should, in their opinion, be classified as ectodermal neoplasms with more or less of the morphologic structure of a chorionepithelioma. This probability is favored by the observations of Schmaus[16] and Michel,[17] each of whom reports one instance of carcinoma of the ovary with areas of tissue resembling chorionepithelioma. Both patients were young girls. The chorionepitheliomatous character in Michel's case was especially prominent in the metastatic nodules. Schmaus did not consider his case to be of teratoid origin but could not absolutely exclude that possibility.

We may apparently divide extra-uterine chorionepitheliomas into two classes, placing in the first class the tumors associated with pregnancy, and in the second, those tumors in which chorionepitheliomatous proliferation develops in a teratoma. A recent paper by Bostroem[18] introduces a new interpretation of the origin and development of chorionepithelioma; and were his suggestion acceptable the above-mentioned classification would lose significance. Although Bostroem's theory is most hypothetical, being based on many suppositions, and although it disagrees with all laws of pa-

thology, nevertheless it may be briefly summarized. According to Bostroem the tumor does not originate from chorionic cells but rather from mesenchymal endothelial cells, the so-called serotinal wandering cells. The author considers these cells undifferentiated germ cells and believes that they are the basis of all formative changes. Irritated by humoral influences these cells react by proliferation and form so-called primary tumor cells which by a process of amitotic division become syncytial cells, the latter by further differentiation giving rise to Langhans cells (Marchand). The Langhans cells may undergo but a single mitotic division, after which no further cell division occurs. Bostroem believes that the differentiated cells can no longer divide and that they die quite rapidly. This explains to him the necroses common in the central portions of the tumor. Marchand's observation of the tendency of syncytial cells to grow in regions adjacent to capillaries and subendothelially is also differently interpreted by Bostroem since, according to the latter, the syncytial cells are formed primarily in these localities, new capillaries proliferate in the vicinity of the tumor and new syncytial cells continually form from serotinal wandering cells; the tumor thus growing in a certain sense by apposition. He further has no difficulty in convincing himself that the "metastases" are not products of a primary tumor but are the result of an irritative action on undifferentiated germ cells in other organs, similar to that causing the primary tumor. In this sense "metastases" are "sister tumors." We shall not attempt a discussion of Bostroem's paper. In spite of the omnipresence of his undifferentiated germ cells, these facts remain: (1) The great majority of chorionepitheliomas develop after pregnancy and especially after mole; (2) chorionepitheliomas developing without previous pregnancy are exceedingly rare; (3) morphologically the tumors resemble chorionic elements, and (4) although Bostroem believes there is no connection between tumor and chorionic cells distributed by the blood stream, the observations of Nagy [19, 20] and of Schmorl do not support his view. Bostroem's humoral exciting agent is very hypothetical although certainly some such possibility may well exist; for example, some authors, in view of a tendency toward lutein cyst formation in these cases, trace the tumor to hormonal influences. Again the plasma of pregnant women dissolves syncytial cells, but this solution is not evident in the plasma of cases of chorionepithelioma. However, Bostroem's whole theory

has no firm basis and does not justify abandonment of our classification of ectopic chorionepitheliomas.

Summary of the Literature

A survey of the literature has given us twenty-five cases of ovarian chorionepithelioma; of these, in thirteen there was a history of pregnancy; in seven, pregnancy was probably excluded, and in five, the diagnosis was not established beyond doubt. These cases are tabulated below.

Table I

Chorionepitheliomas of the Ovary after Pregnancy

Author	Age in years	Number of deliveries	Last previous delivery or abortion	Localization	Remarks
Seitz [22]	27	5	2 months	ovary	no necropsy
Iwase [23] (first case)	31	2	3½ months	ovary	uterus examined by curetting
Iwase (second case)	43	10	1 year	left ovary metastasis right ovary	
Klotz [24]	30	6	1½ years	right ovary	
Voigt [25]	43	4	12 years	left ovary	
Fairbairn [26]	25	3	2 years	left ovary	
Sunde [27]	?	?	?	ovary	
Risel [28]	25	3	8 months	right ovary	
Dougal [29]	29	2	1 year	right ovary	
Ries [30]	48	1	10 years	right ovary	
Kynoch [31]	29	multipara	8 weeks	left ovary	
Phillips [32]	25	1	2 years	right ovary	
Kleinhans [33]	?	?	?	ovary	

Table II

Chorionepitheliomas of the Ovary without previous Pregnancy

Author	Age in years	Localization	Remarks
Lubarsch [34]	13	tumor of the abdomen connected with the uterus	no necropsy
Rosner-Glinski [35]	18	ovary	
Pick [6] (first case)	30	dermoid of ovary with chorionepitheliomatous proliferation	tubal pregnancy
Pick [7] (second case)	9	teratoma and chorionepithelioma	
Varo [36] (first case)	18	right ovary	
Varo (second case)	26	left ovary	
Kaufmann [37]	?	ovary	

TABLE III

Questionable Ovarian Chorionepitheliomas

Author	Age in years	Localization	Remarks
Michel[17]	16	cancer of ovary chorionepitheliomatous metastases	
Schmaus[16]	16	cancer of ovary resembling chorionepithelioma	
Bock[38]	13	chorionepithelioma originating from ovarian cyst	
Massabuau[39, 40] (two cases).	?	cancer with chorionepithelioma-like parts	

I. PRIMARY OVARIAN CHORIONEPITHELIOMA

Report of Case

CASE I. (*Clinical report.*) A woman aged 26; one child living; no history of abortion; date of last delivery unknown. Onset of illness marked by violent headaches and severe left facial pain four weeks before admission. Two weeks later difficulty in swallowing and regurgitation of food through the nose. On entry, weakness, difficulty in swallowing, vertigo. Patient poorly developed and emaciated; skin yellowish; mucosae anemic. Heart and lungs negative; liver 1.5 cm. below costal margin. Examination of nervous system reveals normal eye grounds; eye movements free; right nystagmus; paresis of soft palate; uvula in midline; decreased palatal, patellar and Achilles reflexes; paresis of left recurrent laryngeal nerve. Leucocytes 21,000; red blood cells 2,600,000; hemoglobin 40 per cent; color index 0.77. Death four days later. Clinical diagnosis: brain abscess.

NECROPSY REPORT

The body is that of a poorly developed, emaciated female; the skin is pale and slightly yellowish. Several raised, cyanotic nodules about 0.5 cm. in diameter are distributed over the skin. On incision the nodules are soft, circumscribed and appear quite vascular.

Heart: Negative.

Lungs: Many nodules resembling those in the skin are present in both lungs; and in the lower lobe of the right lung there is a tumor mass about 3 cm. in diameter that projects 0.5 cm. above the pleural surface. This tumor has a spongy consistence, its center is depressed, its cut surface shows grayish to cyanotic mottling and varying sized blood spaces; all in all, the nodule resembles placental tissue.

Kidneys: Both show several small cyanotic nodules.

Liver: The liver edge is somewhat above the umbilicus; the surface is roughened by spongy cyanotic nodules 0.5 to 2 cm. in diameter; in the right lobe there is a large nodule 6 cm. in diameter that closely resembles placenta.

Pancreas: A considerably smaller nodule occupies the head of the pancreas.

Bladder: No neoplastic foci are visible in bladder.

Genital Organs: The uterine cavity is 5.5 cm. long, the mucosa is smooth, and there is no evidence of tumor. The fallopian tubes are thin-walled with patent abdominal ostia. The right ovary measures 2 by 2 cm. and contains a few small cysts. The left ovary measures 6 by 3 cm.; the capsule is grayish and smooth except for a few nodules 0.5 to 2 cm. in diameter. The organ is not adherent to the surrounding structures. On section the entire ovary is composed of cyanotic, cavernous, spongy tissue resembling placenta.

Head: In the skull are three similar nodules; in the brain, which is somewhat edematous, two small cyanotic patches, penetrating the brain to a distance of 2 to 3 mm., are visible over the convexity. Cyanotic, fragile tissue extends into the left sigmoidal sinus, and just posteriorly the dura is pierced by an identical layer 2 to 3 mm. thick. Similar tissue fills the left middle ear; and the lymph nodes about the left carotid artery are likewise involved.

Microscopic Report

Ovaries: Left ovary is surrounded by a fibrous capsule containing many small vessels and minute hemorrhages. No tumor tissue penetrates the capsule. The greater portion of the ovary consists of necrotic tissue in which the outlines of many vessels and larger blood-filled sinuses are apparent. The vessel walls present a homogeneous structure because of a fibrinous transudate, and in the larger sinuses a fibrin network suggests a thrombus. In these areas are shadows of large cells with a faintly eosin-staining cytoplasm but without nuclei, although some chromatin débris is present. The cytoplasm of some cells contains brownish pigment. Leucocytes with fragmented nuclei infiltrate the necrotic foci. In the periphery of the tumor mass the tissue is satisfactory for study. This tissue is very vascular; many capillaries contain fibrin threads, and in a few larger vessels

thrombi are present. In places the capillary endothelium is swollen and the nuclei are vacuolated. In the meshes of this capillary network are masses of hemorrhagic tissue consisting largely of polygonal cells of different sizes, and in places closely packed together in small aggregates. The nuclei are often swollen or hyperchromatic; the cytoplasm is faintly acidophilic. Many mitotic figures are present, some abnormal in character. Interspersed amid these cells are less numerous, large, deeply staining cells containing two to three or more dark oval nuclei. Their shape is varied; many of these syncytial cells are adjacent to vessels and between the two cell types transitional forms may be seen. Penetration of vessel walls by tumor cells is not observed, but nevertheless large polygonal tumor cells, some with poorly stained nuclei, are found in vessel lumina. No ovarian tissue remains nor is there any suggestion of teratoma.

Kidneys: The centers of the metastatic nodules consist of blood-filled sinuses, fibrin threads and necrotic cells. Living tumor tissue resembling that found in the ovary forms the periphery of the nodule; but here syncytial cells predominate, whereas in the ovary the Langhans cells are more prominent; the syncytial cells are invading between renal tubules; some peripheral lymphocytic infiltration is present.

Pancreas: There is a similar histologic picture; pancreatic tissue is infiltrated by syncytial cells.

Liver: The same tumor structure is present with syncytial cells invading between the cells of the parenchyma. There is a peripheral lymphocytic infiltration with some increase in Kupffer cells but no evidence of transformation of these cells into syncytial cells (Bostroem). The surrounding capillary shows no proliferation.

Lungs: The tumor nodules present a similar appearance as vascular necrotic foci and a periphery of large polygonal mononuclear cells and syncytial cells. The latter infiltrate the surrounding compressed lung tissue. Smaller areas consist mostly of syncytial cells with a few scattered Langhans cells. In one medium-sized vessel both types of tumor cells are found in the clot.

Genital Organs: Examination of numerous portions of vagina, uterus, tubes and parametrial structures fails to reveal tumor or evidence of decidual reaction. The right ovary shows follicles, corpora albicantia and a few serous cysts with lutein cells and proliferating theca cells in their walls.

Discussion

What conclusion may one draw from this case? May we call it one of primary ovarian chorionepithelioma? There are three possibilities: (1) Chorionic elements were deposited in the left ovary, liver, lungs and other organs without there having been a primary uterine tumor, and these deposits have given rise to multiple tumors; (2) there was at one time a primary uterine tumor which metastasized, whereupon the primary tumor either healed or was expelled; (3) the ovarian tumor is primary and the other nodules metastatic. In this latter event it may be variously interpreted.

It is very difficult to confirm any one of these three possibilities. The first seems most unlikely, as it is hard to imagine such numerous deposits of chorionic material all giving rise to tumors. Nor can we definitely exclude the second supposition since we know (Münzer [21]) that ovarian metastases of uterine chorionepitheliomas, though rare, do occur. In our case, with metastases so numerous, and with one ovary so completely involved, we should expect both ovaries to be invaded, but on the contrary, the other ovary contained no tumor tissue. The ovarian tumor mass was single, discrete and encapsulated and was the only genital localization of a characteristically genital neoplasm. We, therefore, consider it justifiable to regard it as the primary tumor.

As a primary ovarian tumor it may have originated (1) after pregnancy — like an ectopic chorionepithelioma; (2) as a one-sided development of a teratoma; (3) in connection with an ovarian pregnancy. The first supposition might or might not presuppose previous mole or uterine tumor expelled by labor, leaving no trace. The second hypothesis is difficult to exclude since Pick has been able to demonstrate this possibility. The teratomatous portion may have undergone necrosis; nevertheless, in testicular chorionepitheliomas, teratomatous portions, especially neuroepithelial portions, are readily demonstrable. We believe that after puberty we may consider chorionepitheliomas as being teratomatous in origin only where such parts can be demonstrated or where pregnancy can be absolutely excluded. Previous to puberty all cases should be regarded as teratogenous.

Klotz [24] regarded his chorionepithelioma as an outgrowth of teratoma but could not demonstrate teratoma; in addition, there

was a history of delivery eighteen months previously. It is probable that he was dealing with ectopic chorionepithelioma. Voigt [25] likewise did not find evidence of teratoma, but since the last pregnancy had occurred twelve years previously, he believed that could be excluded. However, there are cases reported with even longer latent periods, hence his case also was probably an ectopic tumor. It is very questionable whether the cases of Schmaus and Michel (cancer of the ovary with chorionepitheliomatous proliferation), and that of Bock [38] (chorionepithelioma originating from juvenile cystoma of the ovary) are real chorionepitheliomas. The same is true of the observations of Massabuau [39, 40] who likewise reported chorionepitheliomatous foci in two ovarian cancers. The latter author explained the syncytial cells according to the theory of Chevassu,[41] namely that rapidly growing cancer cells penetrate blood vessels and, due to their intimate vascular connection, become transformed into syncytium-like cells. Pick found an ovarian dermoid with chorionepitheliomatous proliferation and in addition a tubal pregnancy of the same side. Pick considered the case primarily teratogenous but Risel [28] pointed out that penetration of a preëxisting dermoid by chorionic tissue from the tubal pregnancy could not be excluded. The third supposition (relation to ovarian pregnancy) may now be considered: Kleinhans could not exclude ovarian pregnancy in his case; Sunde regarded his as having developed from an ovarian pregnancy because he actually found villi. In our case we have neither evidence of teratoma nor ovarian pregnancy, therefore, we must regard it as one of primary ectopic chorionepithelioma following a previous pregnancy. Whether or not a mole existed at the time we cannot tell; but from the work of Marchand and Pick, which is supported by many observations, we know that ectopic chorionepitheliomas may occur even after normal pregnancy.

II. Primary Chorionepithelioma of the Liver

There is very little in the literature on primary chorionepithelioma of the liver. Gurewitsch [42] reported the first case as follows: Patient, a woman, 31 years of age, died eighteen months after a hydatidiform mole. Tumor nodules were found in the liver, one invading the small intestine. Other neoplastic foci in lungs and mesentery. No evidence of tumor in the uterus but decidual changes present; lutein cysts in the ovaries.

A second instance was reported by Fischer.[43] The patient, aged 45 years, had had two deliveries, the last eighteen months previous to admission. Necropsy disclosed numerous nodules in the liver varying from 2 to 6 cm. in diameter. There was tumor invasion of the hepatic veins. One similar nodule was present in the head of the pancreas. Microscopic examination revealed a typical chorionepithelioma. The uterus contained no tumor, nor was any found in the lungs. No teratomatous portions were demonstrable. The author believed that the tumor was related to the last pregnancy and that chorionic elements had become deposited in the liver and developed by a process of retrograde metastasis. The last mode of transmission is favored by Fischer in view of the frequency of retrograde spread in chorionepitheliomas of the vagina. Christeller and Oppenheimer [44] observed in a woman 52 years of age, with a history of ten normal deliveries, the last of which dated back twelve years, a liver weighing 2000 gm., filled with chorionepitheliomatous nodules, the largest 6 cm. in diameter. Smaller foci occurred in the lungs and intestinal wall. No uterine tumor was found; the uterine mucosa showed decidual changes, and lutein cysts were present in the ovaries.

Stoy [45] found chorionepitheliomatous nodules in the liver of a man of 40 years; metastases (regarding the large liver nodule as primary) were present in lungs, gastric and intestinal mucosae, spleen and perihepatic nodes. No testicular tumor could be demonstrated. The author regarded the case as an overgrowth of chorionepitheliomatous elements in a liver teratoma but did not find a teratoma histologically. Serial sections, however, were not examined.

Albrecht [46] found chorionepitheliomatous portions in a case of hepatic teratoma but nevertheless does not regard it as true chorionepithelioma. Marx [47] described one case of angioplastic liver sarcoma, that of a man 52 years of age. This case is mentioned because Bostroem [18] regarded it as one of chorionepithelioma. Our examination of Marx's paper gave us no evidence for such a conclusion.

Report of Case

Case II. (*Clinical report.*) Patient a woman, aged 46; menses began at 15 and continued regularly up to 35 at which time they ceased; five pregnancies; two children living and well. In February 1920 she observed a small tumor in the right abdominal region which about ten months later occupied the entire

right abdomen. In January 1921 the patient entered the hospital, and a large mass, presumably liver, was found extending 8 cm. below the costal margin. Aside from atrophy the genitalia were negative. Luetic scars on the lower limbs, and a strongly positive blood Wassermann led to a diagnosis of multiple liver gummas and antisyphilitic treatment was begun; the patient, however, became more cachectic and the nodular hepatic tumor increased in size. She died the following month.

Necropsy Report

Peritoneal Cavity: It contains 300 cc. of clear, yellow fluid. The liver is greatly enlarged, the lower pole of the right lobe being 3 cm. above the iliac crest. The transverse colon is adherent to the inferior surface of the liver.

Pleural Cavities: The right pleural cavity contains 200 cc. of clear fluid.

Lungs: Two very small bluish brown nodules lie in the upper portion of the right lower lobe; and the lower lobe of the left lung contains several similar nodules.

Liver: The liver is enlarged to about three times its normal size, and is studded with brownish blue nodules varying from 1 to 7 cm. in diameter. The fresh surface shows that most of the tumor occupies the right lobe which is composed almost entirely of fused irregular areas of tumor tissue; only three small nodules are found in the left lobe. The nodules, which vary considerably in size, are soft, fragile and somewhat spongy. The centers of the larger nodules are yellowish, the outer portions are brownish blue, while the surrounding stroma is fibrous and depressed.

The gall bladder is enlarged and filled with thick brownish bile. A small tumor nodule lies beneath the mucosa in the region of the neck of the gall bladder. The mucosa covering the mass is elevated and soft. There are about fifty small concretions but the bile ducts are patent.

Kidneys: The surface of the left kidney shows one small focus of tumor tissue.

Genital Organs: There is a small hemorrhagic cyst in the left ovary. The vaginal and uterine mucosa is negative.

Microscopic Report

The central portions of the tumor nodules in the liver consist largely of blood-filled sinusoids with much fibrin, giving a thrombus-like appearance. The hemorrhagic necrotic centers are surrounded by zones of tumor cells; these cells are of two types, (1) large polygonal cells with many mitoses and vacuolated nuclei, and often showing an epithelial arrangement, and (2), darkly staining, multinucleated syncytial cells, which infiltrate between columns of liver cells. Both types infiltrate vessel walls where syncytial cells are found beneath the endothelium; the lumen of one of the larger vessels is completely filled with tumor cells. The Kupffer cells show no tendency to proliferate and form syncytial cells, which is contrary to Bostroem's hypothesis. The liver cells between the tumor areas are faintly vacuolated but their nuclei are well preserved.

Lung: The smaller nodules seen in the lung are not necrotic and consist of scattered Langhans and syncytial cells intermingled with blood sinuses.

Discussion

Is this case to be regarded as primary chorionepithelioma of the liver? We believe the affirmative since no primary uterine tumor could be found and since the largest mass of tumor occurred in the liver. The small nodules in the lung and left kidney are most likely metastases of the liver tumor, it being scarcely conceivable that all the masses should be metastases of another undiscovered tumor. We cannot settle without difficulty the origin of the tumor. No teratomatous elements were observed, yet the possibility of such an origin cannot be disproved as the chorionepithelioma may have completely overgrown and masked a teratoma. The patient was pregnant five times, so there is the probability that the tumor is ectopic chorionepithelioma developing in a retrograde fashion as described by Fischer. We do not know the date of the last delivery but from the history there had been no menses for eleven years. Even though this might represent the latent period of the tumor's development, for longer latent periods are on record, it is not an absolute proof against the hypothesis of an ectopic origin.

Summary

1. Two cases of ectopic chorionepithelioma are reported, one a primary chorionepithelioma of the ovary, the other of the liver.

2. In the case of the ovarian neoplasm no other genital focus existed. Metastatic nodules were found in the skin, lungs, kidneys, liver, pancreas, brain and left temporal bone. After discussing the possibilities as to the origin of ovarian chorionepitheliomas, this case is believed to fall into the class of ectopic chorionepitheliomas.

3. In the case of the liver chorionepithelioma no primary genital tumor was found and but few and small metastases were observed in the lungs and in the left kidney; the liver, however, was considerably enlarged and contained huge masses of histologically typical chorionepitheliomatous tissue. No teratomatous elements were demonstrable. The case is likewise, therefore, regarded as one of ectopic chorionepithelioma initiated by the transportation in a retrograde manner of chorionic elements through the inferior vena cava.

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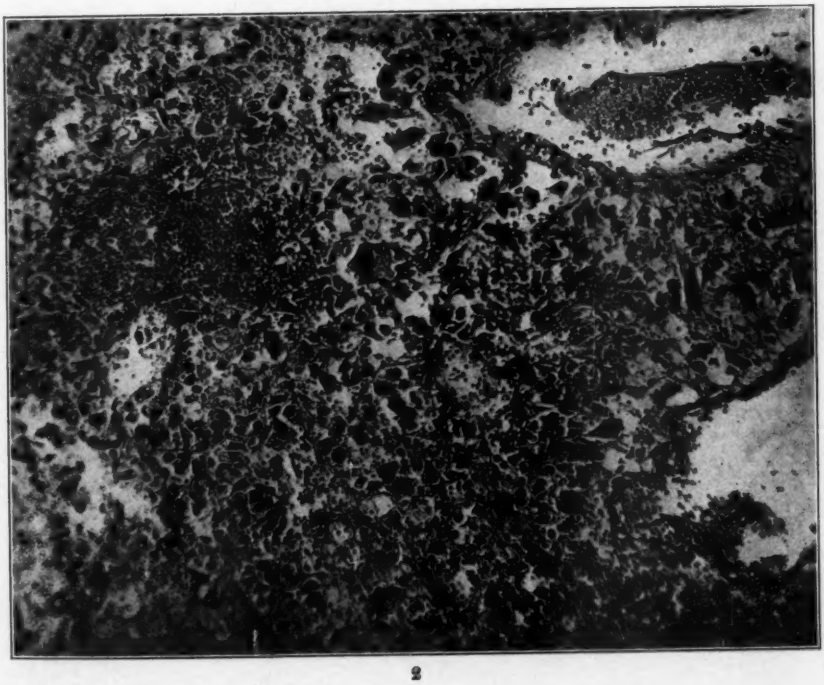
DESCRIPTION OF PLATE

PLATE 18

FIG. 1. Case of primary ovarian chorionepithelioma. Genital organs after hardening in formalin. The left ovary consists of sponge-like tumor tissue.

FIG. 2. Case of primary ovarian chorionepithelioma. Photomicrograph of section from periphery of the tumor of the ovary. Two different types of cells (Langhans and syncytial) are demonstrable, as well as large sinuses filled with blood.

1



2

de Zalka Ectopic Chorionepithelioma

Plate 19

Fig. 3. Case of primary hepatic chorionepithelioma. In the tumor are large sinuses filled with blood and fibrin threads. In the periphery of the tumor are large syncytial cells.

Fig. 4. Case of primary chorionepithelioma of the liver. A blood vessel of the liver filled with tumor cells.

3

4

de Zalka

Ectopic Chorionepithelioma

MUSCLE HEMOGLOBIN IN HUMAN AUTOPSY MATERIAL *

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Experiments in this laboratory have shown that for the dog, muscle hemoglobin is a variable factor.[1] It is in highest concentration in adult active dogs and lowest in young pups. It is probable that exercise is more important than the level of the blood hemoglobin in determining the hemoglobin concentration in muscle fibers. Severe long-continued anemia in dogs may reduce the muscle hemoglobin level somewhat, but in healthy anemic adult dogs it rarely falls below 400 to 500 mg. muscle hemoglobin per 100 gm. We may observe lower normal values in quiet, confined, non-anemic, adult house dogs.

A method satisfactory for dogs was described in detail and we thought it would be possible to modify this muscle hemoglobin method sufficiently to give worth-while determinations in human necropsy material. In dogs it is possible to render the muscles practically blood hemoglobin-free by simultaneous bleeding and perfusion, massage and careful washing.[2] There are many difficulties in the necropsy procedure and these results of necessity are not so satisfactory as were the experiments in dogs. Access to muscles is limited in the usual postmortem examination and most of our readings concern the rectus abdominis and adductor longus muscles.

We have shown that in dogs it is necessary to free the muscle of contained blood hemoglobin in order to obtain accurate values, and it must be admitted that only occasionally will necropsy material be found which can be prepared free from blood hemoglobin. Moreover, it is not difficult to show that under certain conditions muscle hemoglobin can be washed out of the muscles by an excess of gravity perfusion. For example a dog perfused on one side immediately after death may be placed in the cadaver ice-box forty-eight hours. The perfusion of the other side with pressure, using the standard glucose salt solution, will give distinctly lower readings in the late

* Received for publication November 20, 1927.

perfused side in spite of the fact that some blood clots still persist in the smaller vessels of these muscles. This indicates obviously that muscle hemoglobin has been washed out of these muscles perfused forty-eight hours after death. It is possible that physical changes in the muscle hemoglobin and muscle fibers due to rigor mortis, accumulation of lactic acid or other factors are in part responsible for this escape of muscle hemoglobin in the perfusion fluids.

In spite of these many difficulties we decided to proceed with a study of the human material. Care must be used in the interpretation of results and no emphasis can be placed upon minor variations in the muscle hemoglobin readings, but we believe the larger variations in muscle hemoglobin values do have some significance. It is significant that these human values and abnormalities coincide with the more easily controlled observations in dogs. It appears that the level of muscle hemoglobin in man as in the dog is very largely determined by exercise or work done. Probably low blood hemoglobin values and diet factors have some little influence on the level of muscle hemoglobin.

Method

The results reported herein were compiled using the adductor longus and the rectus abdominis muscles. A few minor modifications were made in the method during the study, but essentially the method employed at all times was to wash through the right external iliac artery 4000 cc. to 7000 cc. of 1 per cent sodium chloride plus 5 per cent glucose solution. This washed out the blood in the vessels in the right leg and the right rectus abdominis. The muscles were not massaged either *in situ* or after removal as it invariably caused an increase in the amount of edema. It was also found that the washing if done slowly with a moderate amount of pressure was more satisfactory than if done quickly with high pressure. A four-liter bottle was used and the pressure supplied by a hand pump. It was not unusual to take from twenty minutes to one half-hour for the actual washing. Of the utmost importance was the length of time which had elapsed since death. In those cases in which the blood had clotted in the vessels it was impossible to remove any great amount of blood, and even small amounts of perfusing fluid

gave edema, while larger amounts frequently seemed to wash out a certain amount of muscle hemoglobin.

The right side having been perfused, approximately 30 gm. samples were removed from both adductor longus and rectus abdominis muscles, the left being kept as controls. In taking these sections due care was exercised to avoid contamination of the muscle with blood, all vessels being ligated before cutting. At first, samples were taken from each of the four muscles for microscopic examinations as to the blood content. Later sections were taken only from the muscles which had been perfused. Microscopic sections have shown that in nearly every case there is much less blood in the capillaries of the perfused side than in the unperfused side, and in some cases the perfused capillaries are entirely clear of red blood cells.

The remaining portions of the muscle were trimmed free from fat, fascia and any large blood vessels and were then chopped moderately fine with a razor blade, using this method to cut the fibers without crushing them. Duplicate 10 gm. samples from each muscle were taken and 40 cc. of 0.4 per cent ammonium hydrate added to each. The remainder of the chopped muscle was set aside temporarily. The ammonia extract was thoroughly stirred and placed in the icebox at 4° to 7° C for sixteen hours. During this time the extract was thoroughly stirred two to three times. It was now either filtered or centrifugalized. If filtered it was first put through a wire gauze strainer, then several thicknesses of cheesecloth and then through double thickness of filter paper giving a clear filtrate. Centrifugalization at high speed for twenty minutes and removal of the supernatant fluid by pipette gave equally clear solutions and was especially advantageous in those muscles particularly rich in fat. In cases in which the centrifugalized fluid was not absolutely clear it was put through filter paper. The filtrate was a 20 per cent extract of the muscle, and because of the dilution was unsuitable for analysis by the oxygen capacity method of Van Slyke, the percentage of error due to the physically dissolved oxygen being too high.

Three different quantitative colorimetric estimations of pigment were utilized. The clear extract was examined in the spectrophotometer and the concentration estimated from the density. Kennedy,[3] and Kennedy and Whipple [4] have discussed the relation between the concentration of hemoglobin and its optical density and the identity

of blood hemoglobin and muscle hemoglobin. Small portions of the extract were taken and the oxyhemoglobin changed to carbon monoxide hemoglobin by bubbling illuminating gas through the solution. This was then read in a Duboscq colorimeter against a 1 per cent solution of dog's blood, the hemoglobin content of which had been determined by the Van Slyke method. There was frequently some difficulty in matching the solutions, the muscle hemoglobin seeming to have a slightly more yellow tint than the blood standard. To obviate this difficulty a Wratten light filter No. 74 was

TABLE I

Comparison of Hemoglobin Values on Identical Muscle Samples Estimated by Different Methods. Muscle Hemoglobin Expressed in Mg. per 100 Gm. Muscle.

	Acid hematin	CO hemoglobin		Spectrophotometer	Average
		No filter	With filter		
Left adductor not perfused.....	1190	1425	1035	1270	1220
	1190	1400	1010	....	....
Right adductor perfused.....	870	810	730	835	815
	880	790	790	....	....
Left rectus not perfused.....	810	1000	710	780	825
Right rectus perfused.....	600	710	530	570	600
	620	680	470	....	....
Right pectoral not perfused.....	1130	1290	1025	1110	1160
	1210	1380	1000	....	....

placed in the eye piece of the colorimeter. Under these conditions the colors of the solutions were more nearly comparable. Kennedy [5] has discussed the value of these light filters in colorimetry. The remaining portions of the original muscle extract were now changed into acid hematin and read against a similar standard prepared from dog's blood. The solution is prepared as follows: Add 4 drops of 5N hydrochloric acid to 10 cc. of the extract, shake until the precipitate is redissolved, and then place in the ice-box over night.

The pigment content of the muscle of ten cases was determined by using three colorimetric methods; namely the *spectrophotometric*, the *acid hematin*, and the *carbon monoxide hemoglobin* both with and without the aid of light filters. Table I shows the relative agreement of these four methods on one case (A–209). In our hands the determination by the carbon monoxide method was the most troublesome

and it was thereafter dispensed with. All other figures appearing in this paper are averages of determinations by the acid hematin and the spectrophotometric methods, each of these usually made by a separate observer * and all of them averages of duplicate examinations.

Since even with the greatest care edema occurred in certain cases it was thought wise to make a correction for this in so far as was possible. From the original chopped muscle, duplicate 1 gm. samples were weighed into weighing bottles and dried to constant weight in a vacuum oven with a temperature of 72° to 76° C and a vacuum of from 23 to 27 inches of mercury. As a rule, at the end of ten hours the specimens were so dehydrated that another six to ten hours drying did not change the weight more than 1 to 2 mg. Correction for edema may be readily calculated from these figures. As there was no assurance that the rectus and the adductor muscles were equally perfused and equally edematous, it was necessary to determine each of them separately on each side and each in duplicate. This method is faulty in many respects because the perfusing fluid itself contained 6 per cent of solids, and there is no assurance that during the perfusion a certain amount of protein might not have been washed out of the muscles. So in addition to estimating the relative dry weights of the different samples the amount of nitrogen was determined on the dried samples by the Kjeldahl method. On this basis the protein content was estimated and a correction established for the edema. In practice, for any pair of muscles, we usually averaged the factor obtained by comparing the dry weights and the factor obtained by comparing the protein content, and used this average factor to correct for edema of the muscles. Table II (page 80) illustrates the points mentioned.

Usually the correction factor is greater than 1. It is always greater than 1 where there is edema due to perfusion. However, in a certain percentage of our cases the correction factor is less than 1. For example, in a case such as A-296 where death was due to myocardial failure with marked anasarca, it is probable that the hypertonic perfusing solution caused absorption of fluid from the tissues.

It may be recalled that the spectrophotometric curve of the absorption bands of muscle hemoglobin is just slightly but definitely

* We wish to acknowledge the assistance of Miss Beatrice Moshier, who made most of the acid hematin readings.

different from that of blood hemoglobin, as pointed out by Kühne,[6] Günther[7] and others. The difference is that the points of maximum absorption of each of the two main bands in the muscle hemoglobin are moved about 5 microns toward the longer wave end of

TABLE II

Method of Calculating Correction for Edema in Perfused Muscle (A–258)

1. COMPARISON OF DRY WEIGHTS

		Wt. of muscle in gm.	Dry wt. in gm.	Per cent dry weight	Average		
Right rectus perfused	A ...	0.824	0.172	20.9			
	B ...	0.976	0.202	20.7	20.8	25.0	1.2
Left rectus not perfused	A ...	0.702	0.174	24.8		20.8	
	B ...	0.641	0.161	25.1	25.0		

2. COMPARISON OF PROTEIN CONTENTS

		Wt. of muscle	Protein in gm.	Per cent of protein	Average		
Right rectus perfused	A ...	0.824	0.139	16.9			
	B ...	0.976	0.160	16.3	16.6		
Left retcus not perfused	A ...	0.702	0.155	22.1		21.7	1.31
	B ...	0.641	0.137	21.3	21.7	16.6	1.2
							1.25 Av.

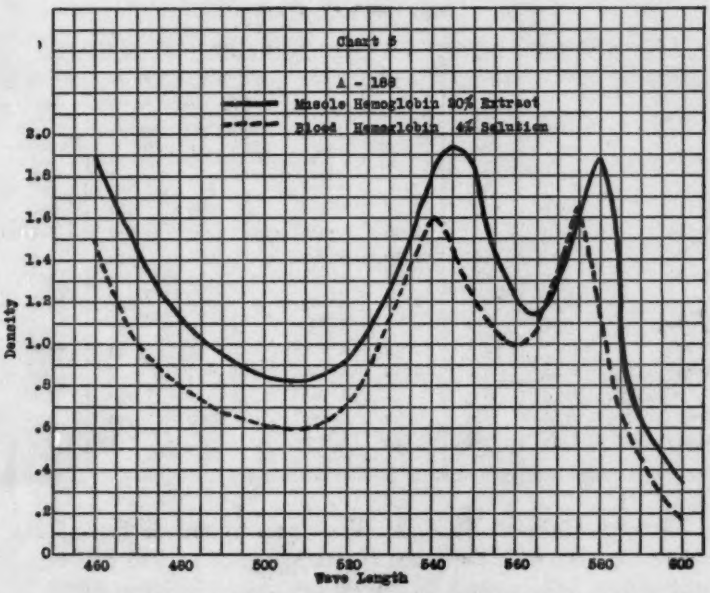
3. CALCULATION OF HEMOGLOBIN CONTENT IN MG. PER 100 GM. OF MUSCLE

	Duplicate samples	Right rectus perfused	Average
Spectrophotometer.....	A	770	
	B	760	765
Acid hematin.....	A	730	
	B	720	725
			745 × 1.25 = 930 mg. of hemoglobin per 100 gm. muscle corrected for edema.

the spectrum. This fact gives us an opportunity to test in a gross way the importance of the blood hemoglobin in the capillaries in any given muscle sample. Chart 3 presents the curves of the blood

hemoglobin and muscle hemoglobin from the same case (A–188). These curves are presented as they are entirely typical of the hemoglobin from the two sources. In this particular case the blood hemoglobin was estimated one month before death. The two readings were made by separate observers. The muscle hemoglobin was estimated from an unperfused muscle which still contained blood in the

CHART 3



The Curves of the Blood Hemoglobin and Muscle Hemoglobin (A–188)

capillaries. It will be seen, however, that this particular case was one of very severe anemia and the hemoglobin content of the blood was much lower than normal. However, we have repeatedly observed this same type of muscle hemoglobin curve in both the perfused and unperfused muscle.

That there is a noticeable difference between the perfused and unperfused side is shown by Table IV which gives the values of the perfused side for the adductor longus as illustrated above. Except in three instances the corrected value for the perfused muscle is lower than that of the unperfused side. The average of these is

around 10 to 15 per cent below the value of the unperfused muscle. It must be admitted that perfusion rarely removes all of the contained red cells so that this correction is an inaccurate variable. In three instances the corrected value of the perfused muscle is greater than that of the unperfused side. This point is discussed above and is probably largely due to the hypertonic perfusate in the presence of tissue edema of disease.

TABLE IV

Muscle Hemoglobin before and after Perfusion. Mg. per 100 gm. of Muscle

No.	Leg unperfused	Leg perfused	Leg perfused; corrected for edema	No.	Leg unperfused	Leg perfused	Leg perfused; corrected for edema
X-670.....	1010	805	....	A-268.....	975	860	840
A-172.....	1000	630	....	A-274.....	1050	900	900
A-188.....	1140	940	1000	A-280.....	1225	670	840
A-198.....	960	930	970	A-281.....	600	650	590
A-204.....	820	615	690	A-282.....	540	580	580
A-209.....	1230	860	1120	A-283.....	970	990	1030
A-253.....	750	790	....	X-835.....	570	550	550
A-254.....	1095	945	1040	A-285.....	1170	1100	1050
A-258.....	1160	910	1090	A-295.....	800	510	550
A-260.....	1015	855	....	A-296.....	670	660	590
A-262.....	1180	740	930	A-297.....	1050	1000	990
A-267.....	795	370	550				

Necropsy Material. In Table V we present muscle hemoglobin values together with the cause of death, age of patient and blood hemoglobin. The values for the blood hemoglobin and all other data pertaining to the patient we have obtained from the clinical history. The blood hemoglobins are recorded on the basis of the Sahli standards. It will be noted that the values range all the way from 550 mg. to 1120 mg. of hemoglobin per 100 gm. of muscle. In comparing the relationship between blood hemoglobin and muscle hemoglobin it is interesting to note that seven of sixteen cases have blood hemoglobin of 75 per cent or below. Of these seven only three have muscle values in the lower half of the group and the remaining four have muscle values in the high upper part of the group. In fact the highest muscle value obtained had a blood hemoglobin of 70 per cent while the two lowest blood hemoglobins, 30 per cent and 43

per cent, have very high muscle hemoglobin values, 1090 and 1000 mg. respectively. These two cases are quite remarkable; the lower value of 30 per cent hemoglobin was found in a case of rapidly

TABLE V

Muscle Hemoglobin as Related to Blood Hemoglobin. Cause of Death, and Age of Patient

Case No.	Muscle hemoglobin *		Age	Blood hemoglobin per cent	Red cell count	Cause of death
	Adductor	Rectus				
A–267 ...	550	490	72	80	4,250	Combined sclerosis. Bronchopneumonia.
A–295 ...	550	475	58	60	2,400	Colitis. Starvation.
A–282 ...	580	550	58	77	4,910	Carcinoma of breast.
A–296 ...	590	...	53	90	....	Myocardial failure.
A–281 ...	590	...	77	84	....	Arteriosclerosis. Chronic nephritis.
A–204 ...	690	...	56	65	....	Perinephritic abscess. Starvation.
A–253 ...	790	710	57	90	....	Arteriosclerosis. Lobar pneumonia.
A–268 ...	840	...	41	70	2,800	Alcoholism. Pneumonia.
A–274 ...	900	670	55	84	....	Carcinoma of trachea.
A–262 ...	930	950	13	92	5,570	Scarlet fever. Bronchopneumonia.
A–198 ...	970	870	10	75	4,568	Pneumococcus meningitis.
A–188 ...	1000	1030	4.5	43	2,600	Aplastic anemia.
A–283 ...	1030	750	15	78	4,800	Post diphtheritic paralysis and bronchopneumonia.
A–254 ...	1040	...	32	95	4,650	Lobar pneumonia.
A–258 ...	1090	970	25	30	1,740	Aplastic anemia.
A–260 ...	1100	820	38	70	3,810	Post scarlatinal nephritis.
Additional cases in which blood values are not available						
X–835 ..	550	...	60	..	....	Cirrhosis.
A–205 ...	620	...	43	..	....	Cirrhosis. Lobar pneumonia.
X–670 ..	805	625	45	..	....	Fractured skull.
A–280 ...	840	...	51	..	....	Strangulated hernia. Peritonitis.
A–297 ...	990	...	66	..	....	Carbuncle. Septicemia.
A–285 ...	1050	790	27	..	....	Syphilitic menigitis. Basilar hemorrhage.
A–209 ...	1120	770	40	..	....	Diffuse bronchopneumonia.

* Hemoglobin in mg. per 100 gm. of muscle. Values of perfused muscle corrected for edema.

developing aplastic anemia (A–258). The entire duration of the illness was three to four weeks in an active young woman, 25 years of age. The other case in this group is an unusual one of a young child

4½ years old who had been confined to his bed during most of a severe months illness. We should not expect such a high reading here for two reasons, first, age, and second, the long stay in bed. However, there is an interesting factor present; this patient had twenty-one transfusions of 50 to 150 cc. of blood within five weeks. There was much blood pigment in the endothelial phagocytes of the lymph nodes and spleen. It is probable that this greatly increased blood destruction and storage of pigment have been in some part responsible for this increase in muscle hemoglobin.

We hope to measure the muscle hemoglobin in cases of pernicious anemia as it is generally observed that the skeletal muscles are often very deep red in these cases. It is interesting to note that the case with the lowest muscle hemoglobin had a blood hemoglobin of 80 per cent. There are several cases with low muscle hemoglobin values which also have moderately low blood hemoglobin, 70 to 85 per cent, but these are usually in inactive individuals. Although this series of sixteen cases in which the blood findings are known is entirely too small to allow us to draw general conclusions, nevertheless the figures agree with those recorded in dogs and indicate that severe anemia causes only a slowly progressing slight decrease in the muscle hemoglobin.

Table VI is a redistribution of Table V showing the muscle hemoglobin values both in the acute and chronic diseases. In the thirteen necropsies in which we have listed an acute illness as the cause of death the average muscle value is 980 mg. of hemoglobin per 100 gm. of muscle. The lower values in this group are from, (1) an obese alcoholic, 45 years old, no occupation, who sustained a fractured skull; (2) an obese woman, 51 years old, who was also a diabetic and who died following an operation for a strangulated hernia; and (3) an emaciated woman of 41 "who looks much older," who was a drug addict and had suffered from pain and stiffness in the joints for several years. With the exception of these three patients, this group was fairly active, most of them young or middle-aged. In this group we have included a patient having carcinoma of the trachea; who died from obstruction and who had been fairly active until shortly before death.

Of the ten chronic diseases listed, the average hemoglobin value is 651. Not including the aplastic anemia of four weeks duration noted above it would be 620. The three lowest values listed were,

(1) a case of combined sclerosis who had been bedridden for seven months; (2) an obese habitual drunkard of 66 who had been doing no active work; and (3) an extremely emaciated woman of 54 who died of colitis and starvation. The difference of the muscle hemoglobin values in the acute and chronic diseases is quite striking.

TABLE VI

Muscle Hemoglobin as Related to Cause of Death

	Adductor longus Muscle Hemoglobin *	Average
Acute Diseases		
Pneumococcus meningitis	970	
Lobar pneumonia	1040	
Aplastic anemia	1090	
Post scarlatinal nephritis	1100	
Scarlet fever. Bronchopneumonia	930	
Alcoholism. Pneumonia	840	
Carcinoma of trachea and obstruction	900	
Post diphtheritic paralysis. Bronchopneumonia	1030	
Diffuse bronchopneumonia	1120	
Strangulated hernia, peritonitis	840	
Syphilitic meningitis	1050	
Carbuncle and septicemia	990	
Fractured skull	805	
		980
Chronic Diseases		
Aplastic anemia	1000	
Perinephritic abscess with starvation	690	
Combined sclerosis. Bronchopneumonia	550	
Arteriosclerosis. Chronic nephritis	590	
Carcinoma of breast	580	
Colitis. Starvation	550	
Myocardial failure	590	
Arteriosclerosis. Lobar pneumonia	790	
Cirrhosis. Lobar pneumonia	620	
Cirrhosis	550	
		651

* Muscle hemoglobin values expressed in mg. per 100 gm. of muscle.

Every case with an extremely low value is one in which there is a chronic wasting disease necessitating inactivity.

Muscle Hemoglobin Related to Age. There are four cases in this series below 20 years of age (see Table V). They show high values in the neighborhood of 1000 mg. There are only three cases over 60 years of age. Two of these show low values but both had chronic diseases. The highest values occur in a 40 year-old laborer who had

been working hard until six days before death, and in a 38 year-old well developed man. Other high values occur in patients whose ages are 25, 27, and 32. We believe that here again we observe the result of activity rather than of age itself, for the previously healthy young adults show the highest values.

In conclusion it may be pointed out that the behavior of muscle hemoglobin is very like that of blood hemoglobin particularly as regards the end products formed within the body. It is known [8] that muscle hemoglobin introduced intravenously, intraperitoneally or intramuscularly is promptly excreted in part as bile pigment in the urine. Therefore it will be of much interest to study clinical cases of myositis or other related diseases to obtain evidence as to the quantitative contribution of bile pigment arising in the striated muscles.

Summary

A method is described for the quantitative analysis of muscle hemoglobin in autopsy material.

In twenty-three cases studied, values of 550 mg. to 1120 mg. per 100 gm. of muscle are found.

The muscle hemoglobin is apparently only slightly influenced by fluctuations in the blood hemoglobin.

The highest values are found in active young adults who have died after a short illness.

Low values are found in the chronic diseases and wasting illnesses. In every case in which there is an exceptionally low value there has been prolonged inactivity.

We conclude that in man as in the dog the concentration of the muscle hemoglobin within the muscle fibers is determined more by muscular activity than by the level of blood hemoglobin.

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AN EPITHELIAL CYST OF THE HYPOPHYSIS *

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This case is of interest because it is one of a small group of cystic neoplasms found in the region of the pituitary and because of the presence of an anomalous formation of small cystic cavities in the occipital lobe of the brain.

A comprehensive survey of the literature of such tumors is given by Globus [1] in his report of a teratoid cyst of the hypophysis and by Critchley and Ironside [6] in a discussion of pituitary adamantinomas.

The tumor presented here has the characteristics of the group of neoplasms of the pituitary region considered by Erdheim and others to arise from remnants of the hypophyseal duct. In the embryologic development of the hypophysis two sources of origin are found,[2] one from the primitive mouth, the other from the third ventricle of the brain. The cerebral element scoops out the buccal portion to form a cup; the buccal connection disappears, but the cerebral persists as the infundibular stalk. The presence of two groups of squamous epithelial cells has often been noted on the anterior aspect of the infundibulum and on the anterior lobe of the pituitary. These are believed by Erdheim and others to be remnants of the hypophyseal duct, and the origin of certain cysts of the hypophysis.[6] These tumors are lined with squamous epithelium, and may show variations in the type of growth, such as the formation of a "basal cell" type of carcinoma or of an adamantinoma.

REPORT OF CASE

Clinical History: The patient was a male English-American hatmaker of 48 years, who had been subject to sick headaches all his life. He had gonorrhea in 1897. In 1922 he first noticed dizziness. The present illness began in September, 1926, when he had a headache for three weeks; at the end of that time he had nausea and vomiting and was in bed for one week with what the local physician called "grippe." After this he was often drowsy and if he leaned over,

* Received for publication November 18, 1927.

became pale. About October 17 excessive urination, accompanied by great thirst, were first noticed. Both of these symptoms became progressively worse. There was also a loss of sexual desire. On February 23, 1927, he became emotionally unstable and after this the headache, nausea and vomiting became aggravated. On February 24 he was sent to a general hospital, where he remained six days, and was then transferred to the Boston Psychopathic Hospital.

Summary of Physical Examination: A rather emaciated man, with protruding underlip, who was so restless and uncoöperative that examination was difficult. Hair distribution and skin were normal. Circulatory and respiratory systems were negative. The pupils were unequal but reacted slightly to light and accommodation. Ophthalmoscopic examination showed that the disc margins were not clear, vessels were normal, no hemorrhages were seen. Visual fields roughly normal. (The patient's coöperation was poor.) The epigastric reflex was less active on the right than the left side and the right abdominal was absent. The knee jerks were equal and active. Sordes on lips. A slight temperature increase was present from admission onward, though no cause for this could be found. A provisional diagnosis of left-sided cerebral tumor, probably abscess, was made. X-ray plates of the sella turcica were negative on two examinations and though the symptoms suggested pituitary disease, physicians were loath to make a diagnosis of pituitary tumor with two negative X-ray reports.

After six days in the hospital he became excited, refused to eat and was tube fed until the time of his death, nine days after admission. March 11, 1927, he died, one and a half hours after a tube feeding. The total duration of symptoms was about six months.

Necropsy Report

The skull, dura and convex surface of the brain were negative. The pituitary was soft, fluctuant, about three times its normal size and bulged upward out of the sella turcica. On removing the hypophysis from the brain, soft gelatinous yellow material oozed out of the infundibulum. It was difficult to define grossly the exact location of the cyst in relation to the lobes of the pituitary. No distortion of the structures at the base of the brain was present. The opening of the sella turcica did not appear enlarged, the floor, however, was brownish red, roughened and eroded.

Other findings were marked edema and congestion of lungs, passive congestion of spleen, and a chronic inflammatory nodule of the right testis with old adhesions to the tunica vaginalis.

Microscopic Report

The cyst was fixed *in toto* in formalin and serial sections were made which were stained with hematoyxlin and eosin, Scharlach R and Van Gieson's stains. It was lined with stratified squamous epithelium with long papillary projections. On some portions of

the surfaces of the papillary projections rather low ciliated columnar epithelium was seen, and in other similar locations there were epithelial cells containing globules like those found in the epithelium of secreting glands. The largest papillary projection and what appeared to be the most actively growing portion of the cyst wall was situated between the anterior and posterior lobes, both of which were compressed by the cyst. Posterior lobe tissue was found in only a small number of the sections. At this point there were numerous gland-like structures resembling the pars intermedia of the pituitary and containing pinkish material staining like colloid. A few of these were seen at other places in the cyst wall. At one point there was a large cholesterin crystal included in a foreign body giant cell. In the cavity were masses of desquamated and disintegrating epithelial cells and polymorphonuclear leucocytes. No sebaceous glands or hair follicles were seen in any part of the cyst wall.

On microscopic examination of the brain another developmental defect was found: In the left occipital lobe several microscopic cysts were seen in the white matter. They were posterior to the lateral ventricle, and no connection with it could be found. The lining of the cysts was made up of cells resembling ependyma. There was considerable variation in the shape and size of the cavities. About the cysts were groups of cells similar to those of the lining but with no opening in the center. There were also dilated thin-walled blood vessels in the same region, but nothing that resembled choroid plexus.

Summary

The cystic tumor described was situated between the anterior and posterior lobes of the pituitary, was unilocular and filled with soft yellow gelatinous material. It was lined by stratified squamous epithelium which formed papillary projections and which showed a tendency to variation by the presence of ciliated cells and cells containing secretion. No hair follicles or epithelial pearls were found, and no areas of calcification, or structures derived from any type of tissue other than epithelium were present.

The histologic appearance places the tumor in the group which Ewing[3] designates as traceable to remnants of the hypophyseal duct. It resembles more the simple cysts of Duffy's Group I,[5] than the adamantinomas or carcinomas.

The character of the symptoms, such as disturbance of heat regulation, polyuria and thirst may have been due to pressure on the base of the brain in the para-infundibular region. Bailey and Bremer [4] in experimental diabetes insipidus concluded that lesions of the para-infundibular region of the hypothalamus may produce polyuria, thirst, cachexia and even rapid death as well as disturbance of heat regulation, and changes in the pulse and respiratory rate.

Another defect, quite probably a developmental anomaly, was present in the white matter of the left occipital lobe of the brain.

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DESCRIPTION OF PLATES

PLATE 20

FIG. 1. Shows the relation of the dermoid cyst to the pituitary structures. Papillary projections covered with squamous epithelium extend into the cavity which is filled with desquamated epithelial cells. × 9.

FIG. 2. From above downwards the layers are as follows: necrotic, desquamated epithelial cells, stratified squamous epithelial cells lining cyst wall; connective tissue backing of cyst with formation of small papillae in places; compressed anterior lobe tissue of pituitary. × 75.

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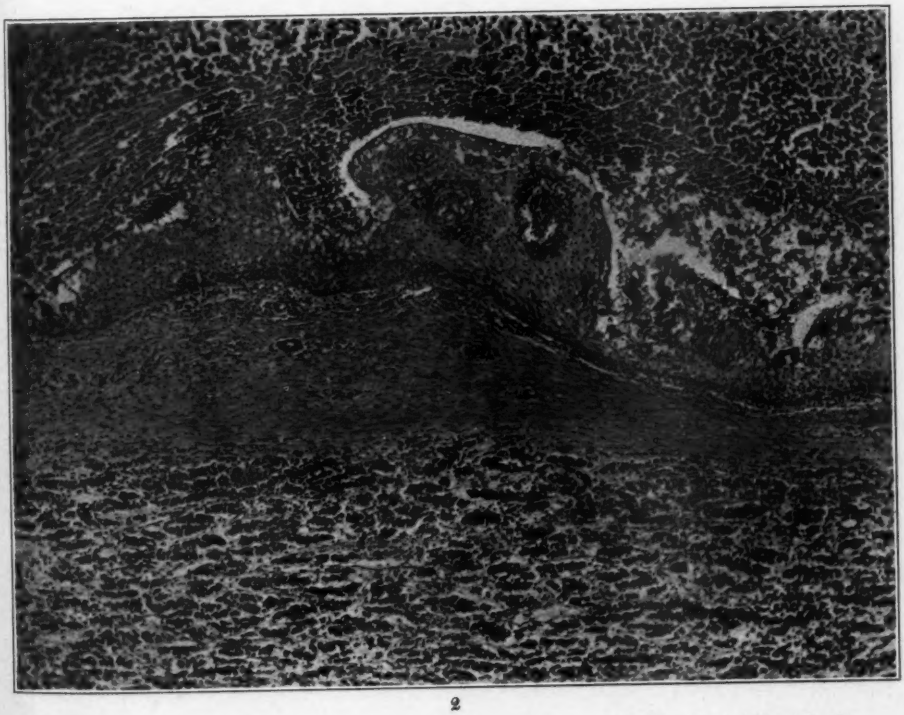

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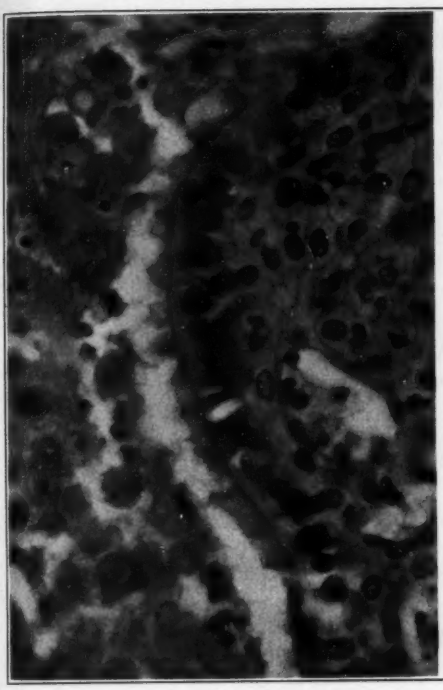
Epithelial Cyst of Hypophysis

PLATE 21

FIG. 3. Ciliated columnar epithelium from the outer edge of a papillary projection. At one side may be seen necrotic desquamated cells and a few polymorphonuclear leucocytes and at the other, stratified squamous epithelium, covered with a layer of ciliated cells and infiltrated with polymorphonuclear leucocytes. × 500.

FIG. 4. Another variation in the type of epithelium lining the cyst; cells containing globules of mucoid secretion. × 500.

FIG. 5. Cystic cavities in the white matter of the occipital lobe of the brain. The cells lining them resemble ependyma. About the large cyst are small clumps of cells similar to those lining the cyst but without lumina. Numerous thin-walled, dilated blood vessels may be seen. × 45.



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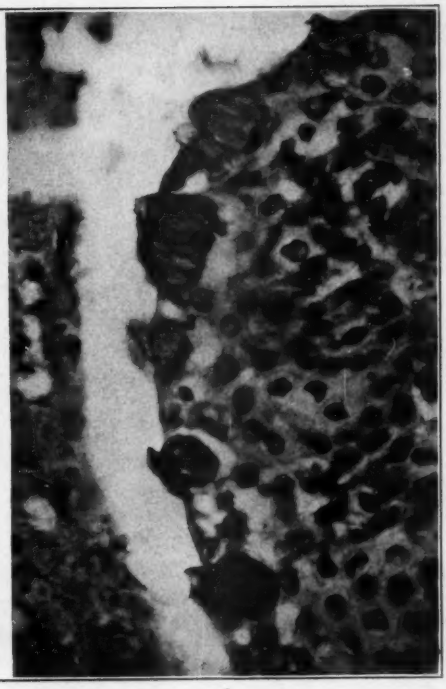

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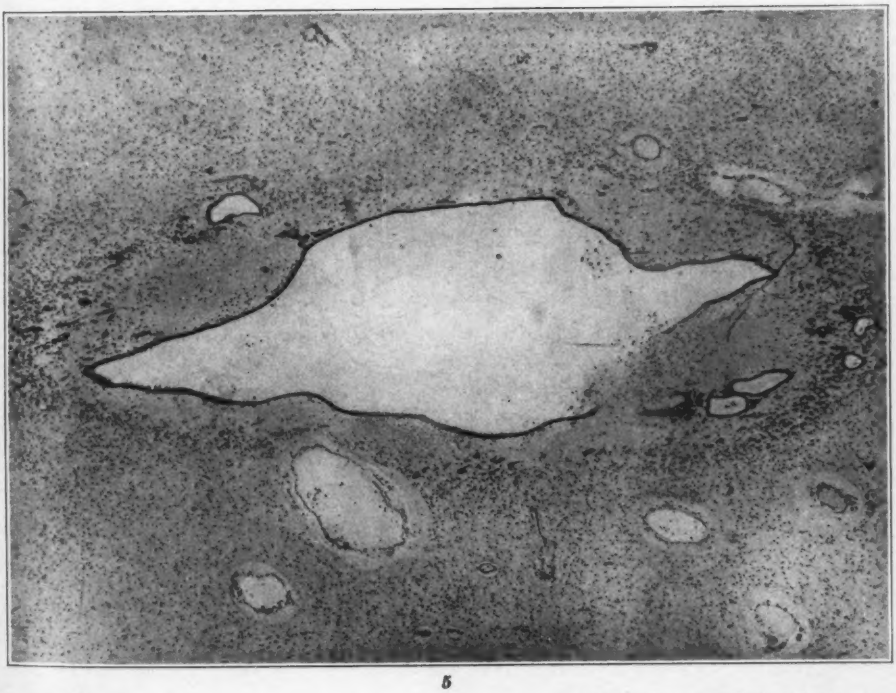

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Epithelial Cyst of Hypophysis